Improvements in cardiovascular risk and physical fitness during cardiac rehabilitation: which improvements are related to reductions in risk for major adverse cardiac events during follow-up?

Outline

The aim of this literature study is to see if cardiac rehabilitation (CR) will improve the cardiovascular (CV) risk factors and physical fitness of patients with Cardiovascular diseases (CVD). Another part of our literature study is the correlation of these improvements in CV risk factors with reductions for major adverse cardiac events during follow-up.

- Contradictory findings were found in all-cause mortality and morbidity. Cardiac-related death was reduced through CR for short and long-term follow-up.
- There is an improvement in exercise capacity, systolic blood pressure, triglycerides concentration, total cholesterol concentration and hospitalization through CR. There was also a reduction in the smoking population up to one year follow-up. Positive findings were found in body composition and fasting glucose.
- Four studies assessed the effect of CR on mortality and on the CV risk factors, two of these studies reported that there could be a reduction in risk for mortality because of the change in systolic blood pressure, total cholesterol concentration and smoking behaviour.

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Context

Our thesis is part of the research domain rehabilitation of internal diseases, in specific CVD. These diseases are a major problem as it is one of the leading causes of death. The occurrence of the diseases is increasing because of the lifestyle that people nowadays have. People exhibit one or more of the following habits, they exercise less, eat more food that contains too much fat and/or sugar, drink too much soda, smoke or have a too high blood pressure. The symptoms that these diseases entail have a major impact on the quality of life. For instance, with heart failure (HF) the exercise capacity will decrease and the patients will experience dyspnoea and oedema. With coronary artery disease (CAD), patients have an increased risk for morbidity, for example cerebrovascular accident (CVA) or myocardial infarction (MI).

CVD arise from the presence of CV risk factors, and some of these are modifiable. Because of the lifestyle we lead, many people do have a worse CV risk profile without paying any attention to it. It is of major importance that in the first place these diseases are prevented by living healthy. When CVD is present, it is even more important to change these CV risk factors in a positive way to reduce the risk of mortality and morbidity. That is where, among other interventions such as education and diet change, exercise training steps in. Exercise training is an important issue in order to prevent these diseases and alter the course of these diseases.

In order to have the greatest improvement in CV risk factors and prognosis it is necessary to exercise specifically. When it is known which CV risk factors are changed by CR, it is possible to focus more on these and find a solution for the CV risk factors that has not been changed by CR. The costs induced due to CVD are enormous. Fifty-three percent of the total cost of CVD's is due to health care (€111 billion), productivity losses account for 26% (€54 billion) and 21% (€45 billion) to the informal care given to patients with CVD's. This gives an estimation of €210 billion a year in the European Union.

For this literature study our promotor already had an investigation question. With the exception that we have specified the population of interest. Only a population with CVD and not a healthy population were included in this study. All the rest of this literature study is done without any aid of the promoter except for some questions that we had. When there were questions, the promoter gave us advice, but not a direct answer so that we had to figure it out ourselves with his advice.

This is a duo-thesis, we did the literature study together. For this thesis, the central format was applied.

We came up with a search strategy together, and both of us selected the articles from titles and abstracts. The abstract, data-extraction, results of study selection, recommendations for further research and conclusion were written by Dennis. Lotte wrote the part "methods" except for the part "data-extraction". Lotte also wrote the outline (except for the bullet prognosis), quality assessment, the reflection of the quality of the studies (strengths and limitations), the reference lists, flow chart, table 1, table 2 and Part II: research protocol (except for the validity and reliability that is written together). The introduction was written together. The results of the data-extraction were split up, each of us described several outcomes. For the discussion, each of us described several outcomes except for the link between prognosis and risk factors, this was written by Lotte. Table 3, 4

and 5 were also made by both of us. The items that were described in the part of limitations and strengths and recommendations were discussed beforehand.

For the investigation protocol, we will use an excel-file that was already made up. In this file, we are collecting all the necessary data. This file has already data from 2013 to 2016, we will complement this file with the remaining data of 2016 and with the data of 2017 and 2018. The data that we gather is coming from doctors and physiotherapists, who do a routine examination. These outcomes are then noted in an online patient file.

PART I: LITERATURE STUDY

1 Abstract

Background: CVD's are a major cause of death. These diseases arise from several CV risk factors, some of which can be counteracted by a CR. As of today, many protocols are used and it is unclear which ones are best suited for CR.

Method: We searched for systematic reviews and meta-analyses in PubMed and WoK which investigated patients with CVD retrieving CR. Reference lists of the included articles were manually searched for additional articles.

Results: After screening on title and abstract we ended up with seventeen articles. Interventions resulted in beneficial improvements in CV risk factors. All-cause mortality and morbidity results were contradictory amongst included articles. Cardiac-related death and all-cause hospitalizations were reduced in the exercise group. There is a correlation between mortality and some CV risk factors for CAD.

Discussion and conclusion: It is clear that CR has beneficial effects. However not all results were clarified. Further research is desirable.

Aim of the study: To analyse the correlation between the change in CV risk factors and which of the improvements in CV risk factors have a beneficial effect on the prognosis of patients with CVD's.

Operationalization: The study will take place at ReGo under supervision of Prof. dr. D. Hansen.

Research question: Improvements in cardiovascular risk and physical fitness during cardiac rehabilitation: which improvements are related to reductions in risk for major adverse cardiac events during follow-up?

Keywords: cardiovascular diseases, heart diseases, vascular diseases, exercise therapy, physical therapy modalities, rehabilitation, prognosis, treatment outcome, cardiovascular risk factors, risk factors.

2 Introduction

The prevalence of CVD's has increased over the last decades, these diseases are a major cause of death. The American Heart Association (2004) found that CVD's are the most common cause of death and hospitalizations. CVD's account for seventeen million deaths worldwide each year, this is almost one-third of the annual death toll (WHO 2008). Although mortality from CVD has decreased in many developed countries, morbidity is still increasing due to improved diagnoses and more successful treatment methods. Therefore, there are more survivors of this disease who still need medical care. There are several CV risk factors which can contribute to CVD's, some of these are modifiable. These modifiable risk factors include exercise capacity, blood pressure, blood lipid concentration, stress, smoking, body weight and insulin resistance/diabetes.

An exercise-based rehabilitation can counteract some of the CV risk factors and reduce the risk of a CV event (Heran et al.2011).

> "CR has been defined as the coordinated sum of interventions required to ensure the best physical, psychological and social conditions so that patients with chronic or post-acute CV disease may, by their own efforts, preserve or resume optimal functioning in society and, through improved health behaviours, slow or reverse progression of disease" (Fletcher et al. 2001).

The USA Centers for Medicare and Medicaid Services has determined that there's enough evidence to support the use of CR after a myocardial infarction (MI), coronary artery bypass graft (CABG), stable angina pectoris, heart valve repair or replacement, percutaneous coronary interventions (PCI) or coronary stenting and heart or heart-lung transplant".

Research over the past forty years has taught us that exercise training, and even (high) intensity interval training, is safe and has many health-related beneficial effects in individuals with CVD (Jollife et al. 2001, Nilsson et al. 2008, Rognmo et al. 2004, Warburton et al. 2005, Wisløff et al. 2007). However, attendance to these rehabilitation programmes is rather low (Leon et al. 2005). Programmes need improvement so patient uptake will be enhanced. This will optimize recovery.

It is thus clear that CR brings a lot of advantages. What is not known yet, is what the correlation between a better prognosis and a positive change in CV risk factors is. When it is known which cardiovascular risk factors are reduced by CR and enhance the prognosis, it is possible to focus specifically on these cardiovascular risk factors. It will also be possible to change the approach of reducing CV risk factors if they do not improve the prognosis.

The aim of the study is to analyse the correlations between the change in CV risk factors and prognosis in patients with CVD's following a CR.

3 Methods

3.1 Research questions

Are cardiovascular risk factors and physical fitness improved by cardiac rehabilitation? And what is the correlation between the prognosis of patients with CVD's and the change in CV risk factors and physical fitness induced by CR?

3.2 Literature search

Articles from PubMed and WoK were retrieved from February to March 2017. Following search terms were used for this search: cardiovascular diseases, heart diseases, vascular diseases, exercise therapy, physical therapy modalities, Cardiovascular risk factors, risk factors, prognosis, treatment outcome and rehabilitation.

Two reviewers independently selected articles on basis of titles and abstracts. From the originally included articles, we independently selected articles from their reference lists. Consensus was made if there was a disagreement.

P: Cardiovascular diseases
I: exercise therapy, physical therapy
C: no exercise
O: prognosis and CV risk factors

We combined our search terms as following:
Pubmed:
((((((Cardiovascular diseases) OR heart diseases) OR vascular diseases)) AND (((exercise therapy) OR physical therapy modalities) OR rehabilitation)) AND ((prognosis) OR treatment outcome)) AND ((Cardiovascular risk factors) OR risk factors)

WoK:
TOPIC:(Cardiovascular diseases OR heart diseases OR vascular diseases) *AND***TOPIC:** (exercise therapy OR physical therapy modalities OR rehabilitation) *AND* **TOPIC:** (Cardiovascular risk factors OR risk factors) *AND* **TOPIC:**(treatment outcome OR prognosis) *AND* **TOPIC:** (systematic review OR meta-analysis)

3.3 Selection criteria

We searched for meta-analysis and systematic reviews. The inclusion criteria were the following: English articles, systematic reviews and meta-analyses, CVD's, outpatient rehabilitation, follow-up studies and human studies. The exclusion criteria were studies that included patients with comorbidities (respiratory conditions like COPD and asthma, kidney diseases, cancer, neurological conditions), cerebrovascular diseases, congenital conditions, subjects with a pacemaker and studies before 1995 (Rauch, et al., 2016).

The exclusion of studies before 1995 was because from 1995 onwards sugary and drug therapy became more established for CVD. These interventions have a big impact on the patients who do CR. Thus, studies from before 1995 are no longer applicable to CR. Rauch, et al., 2016 stated that CR still has an important effect on the prognosis of patients with CVD, even in this era with the surgery and medication that is given to these patients.

3.4 Assessment of quality

Two reviewers assessed the quality of all the included articles by using the SR-RCTs checklist from the Cochrane Handbook for Systematic Reviews of Interventions (Higgins, 2011). A distinction between higher and lower quality of the studies was made through consensus. A lower quality was when four or more questions were inadequately or not described. For the questions used on these checklist, see appendix.

3.5 Data-extraction

Data were manually extracted by both reviewers and checked by each other. We extracted data of the following categories: details of study population (primary diseases), details about the intervention and control group, blood pressure, blood glucose concentration, body measures, blood lipid profile, smoking (CV risk profile), VO_2max. (exercise capacity) and all-cause and disease related mortality, morbidity and hospitalizations (prognosis).

4 Results

4.1 Results study selection

After screening on title and abstract, we included six systematic reviews and meta-analysis in total out of 212 hits on PubMed and no articles on WoK out of thirty-three hits (table 1a). By manually screening reference lists of the included articles, we found an additional eleven articles (figure 1). 239 articles from the electronic databases were excluded. Out of the articles retrieved by electronic databases, seven of them investigated adverse events of exercise therapy, 121 articles investigated a population that did not meet the criteria, 122 articles did not investigate the effects of exercise therapy, 112 articles which were nor a systematic review neither a meta-analysis and 134 did not investigate the right outcomes (table 2). There were no additional results in April 2017 with search strategy.

Nine studies examined patients with (chronic) heart failure with preserved ejection fraction (HFpEF), six studies examined patients with CAD and two studies examined cardio metabolic disorders. Eight studies reviewed the effect of an (comprehensive) exercise intervention versus control/usual care (no exercise group). Comprehensive exercise included aerobic training (walking, cycling, …) and strength training. Three studies examined high intensity interval versus moderate intense continuous training. Participants in most articles were predominantly male, also not many elderly patients were included. Follow-up varied from six months to five years (table 5).

4.2 Quality assessment

The overall methodological quality of the included articles is good (see Table 3). The articles provided enough and adequate information about their search strategy, selection criteria, most important characteristics of their included studies and the aim of the study. All articles were included, even the three articles with a lower quality, this was taken into account when interpreting the results. A big issue is the lack of information about the quality assessment, eight of the seventeen studies did not give any information about this topic. Consequently, we have to be careful when interpreting the outcomes of these studies. Three studies have not done a statistical pooling, with the consequence that we do not have an overview of the results in these studies. Several studies did not describe how they coped with the statistical and clinical heterogeneity. Cornish, Broadbent, & Scheema (2011) did describe how clinical and statistical heterogeneity was handled, but not well enough. Three studies did not mention how the data extraction found place, but they did describe all the important characteristics of their included articles.

The quality of the articles that were included in the systematic reviews and meta-analyses was moderate. The major issue is the limited information about the methodology that is given. The details about the blinding and randomization was missing in most studies. When there was information about blinding, it was mostly not applied because of the nature of the intervention.

4.3 Prognosis

4.3.1 Mortality

Mortality was assessed in twelve of the included articles. This was separated in all-cause and cardiac-related mortality. All-cause mortality was assessed in ten articles. Seven of them did not show a significant difference in all-cause mortality with a follow-up of less than twelve months (Clark, Hartling, Vandermeer, & McAlister, 2005a and 2005b; Davies, et al., 2010a, 2010b; Lewinter, et al., 2015; Sagar, et al., 2015, & Taylor, et al., 2014). Two of them did show a significant reduction in favour of CR (Piepoli, et al., 2004, & Taylor, et al., 2004), this was for CHF and CAD respectively.
For a follow-up longer than twelve months, four articles found no significant difference (Davies, et al. 2010a, 2010b; Sagar, et al., 2015, & Taylor, et al., 2014) while three articles did show a significant difference in favour of intervention (Clark et al. 2005a, 2005b, & Heran, et al., 2011) for patients with CAD and HFpEF. There are two articles with a follow-up of at least five years (Clark, et al., 2005a, 2005b) where they found a significant reduction in favour of exercise for patients with HFpEF and CAD. One study stated zero deaths (Taylor, et al., 2012).

While looking for cardiac-related mortality, one article showed a significant reduction in mortality for a follow-up of less than twelve months (Taylor, et al., 2004). Two articles did also show a reduction of mortality with a follow-up longer than twelve months (Heran, et al., 2011 and Taylor, et al., 2006). These findings were found in patients with CAD.

4.3.2 Morbidity

Morbidity was examined in three of the seventeen included articles. Heran, et al. (2011) stated no significant differences between exercise training alone or in combination with educational and psychosocial interventions in morbidity in patients with CAD for MI, CABG or PTCA. This was the same for short (less than twelve months) and long term (more than twelve months) follow-up. In an exercise based rehabilitation programme versus usual care by Taylor, et al. (2004), there was also no significant difference in a similar population. These findings are not in the same line as the ones found in Clark, et al. (2005b) where they found a statistical difference in re-infarction at twelve months follow-up in patients with CAD in a comprehensive rehabilitation programme.

4.3.3 Hospitalization

As regards to the outcome ‘hospitalization’, the nine studies that investigated this are unanimous. All-cause hospitalization up to twelve months has a difference between exercise and no exercise in favour of exercise. The relative risk ranged between 0.65 (Lewinter, et al., 2015) and 0.85 (Clark, et al. 2005b). None of these studies found a significant difference in hospitalization after twelve months. Some studies also reported a significant reduction in CV-specific hospitalization (Taylor et al., 2014; Sagar et al., 2015; Clark et al., 2005b, & Davies et al., 2010a, 2010b).

4.4 CV risk factors

4.4.1 Exercise capacity

Six of the sixteen studies investigated the effect of CR on exercise capacity. Three of these studies examined the specific effect of interval training. Hwang, Wu, and Chou (2011), and Weston, Wisloff, and Coombes (2014), Cornish, et al. (2011) concluded that both continuous moderate-intensity training (CME) and high-intensity interval training (HIIT) induced an improvement of the VO_2max. in lifestyle induced cardiometabolic diseases and CAD, but HIIT had a significant bigger improvement. Taylor et al. (2012), Lewinter et al. (2015) and Palau, Nunez, Dominguez, Sanchis, and Nunez (2016) found a bigger improvement of the VO_2max. in the exercise group compared to the control group in patients with HF. The mean difference ranged from 3,0 ml/kg/min. (Taylor, et al., 2012) to 3,6 ml/kg/min. (Hwang, et al.).

4.4.2 Blood pressure

Five studies investigated the change in blood pressure with CR. They all found a significant reduction of systolic blood pressure. Only some of them found a difference in diastolic blood pressure. There was a mean difference ranging from 2.0 mmHg (Taylor, Unal, Critchley, & Capewell, 2006) to 12 mmHg (Weston, et al., 2014) for systolic blood pressure. The mean difference for diastolic blood pressure ranged from 2.0 mmHg (Oldridge, 2012) to 6 mmHg (Weston, et al.). The studies that investigated the difference between MCE and HIIT found no significant differences in the reduction of blood pressure.

4.4.3 Blood lipid concentration

Eight of the included studies examined the change of blood lipid concentration. All of these studies reported some improvements. But not all found improvements on the same items. Clark, et al. (2005a, 2005b) concluded that there was a significant improvement of the cholesterol profile in general for patients with CAD.

Two studies found an increase in high density lipoprotein (HDL) for patients with lifestyle induced cardio metabolic diseases and CAD with HIIT in comparison with CME and a control group (Weston, 2014, & Cornish, et al., 2011). However, Oldridge (2012) and Taylor, et al. (2004) reported no change in HDL with CR for patients with CAD. Hwang, et al. (2011) did not found an improvement in HDL for patients with cardiometabolic disease with HIIT compared to CME. Three studies reported on low density lipoprotein (LDL). Oldridge and Taylor, et al. (2004) concluded that there was no significant reduction of LDL with CR for patients with CAD.

Weston, et al. could not make a conclusion because of opposing results for patients with lifestyle induced cardiometabolic diseases. According to four studies (Weston, et al.; Taylor, et al., 2004; Oldridge, & Hwang, et al.) there was a significant decrease of triglycerides, ranging from 0.18 mmol/l (Oldridge) to 0.23 mmol/l (Taylor et al. and Oldridge). According to Hwang, et al. and Weston, et al., there is no difference between HIIT and MCE. Three studies investigated the effect of CR on total cholesterol. CR induced a significant improvement on total cholesterol. According to Oldridge this improvement was mainly seen with a comprehensive rehabilitation. The mean difference ranged from 0.6 mmol/l (Taylor, et al., 2006) to 0.37 mmol/l (Oldridge, & Taylor et al., 2004).

4.4.4 Smoking

Smoking cessation was examined in two articles. According to Taylor, et al. (2004), there was a significant reduction in smoking at one year follow-up in patients who followed a CR programme. However, another study (Taylor, et al. 2006) found no significant difference at a mean follow-up of two years in patients with the same pathology and intervention.

4.4.5 Body composition

Hwang, et al. (2011) tried to show a difference in effect on body composition by comparing HIIT versus CME in patients with cardiometabolic disorders. There was a comparable effect on waist circumference between these two interventions. Both interventions managed to achieve a positive effect on weight reduction but there was no significant difference between these two interventions. There was also no significant difference in BMI (WMD= 0.61 kg/m2; 95% CI= -2.1 to 3.3, P= .66) between HIIT and CME.

4.4.6 Glucose concentration

Comparing HIIT and CME in patients with cardiometabolic disorders, there is no significant difference in fasting glucose (MD= -0.35; CI= -0.87 to 0.16). However fasting glucose tended to improve better in the HIIT group (Hwang, et al. 2011).

5 Discussion

5.1 Quality of the studies

The overall methodological quality of the included studies was good. There were twelve studies with higher quality and five with a lower quality. The average quality of the articles included in the systematic reviews and meta-analyses was moderate because of the lack of information about the methodology.

5.2 Outcomes of the studies

5.2.1 Mortality and Morbidity

We can state that cardiac-related death will decrease with an intervention for patients with CAD, this can be said over relative short-term follow-up (less than two years). A longer follow-up period is recommended in further research. The all-cause mortality is somehow different. Some researchers found a significant difference whilst others did not. Reasons for this contradictory evidence are unclear. Differences in intervention could explain these results.

The contradictory findings concluded from Clark, et al. (2005b), Heran, et al. (2011), and Taylor, et al. (2004) makes it hard to make a conclusion for morbidity. Participants and interventions are similar, follow-up period was equal and methodological quality were very good. More research is needed to further clarify these findings. The overall follow-up period should be prolonged in further research and research for another CVD is desirable.

5.2.2 Hospitalization

It is very clear that exercise training has a major advantage for all-cause and CV-specific hospitalization. But this advantage is only up to twelve months. This is an important finding as hospitalization involves a lot of costs. We can question if these findings can be decelerated by the possibility that the adherence for exercise training weakens after a year of training. Or maybe the exercise protocol has to be changed frequently to keep inducing improvements.

5.2.3 CV risk factors

There is an improvement of the VO_2max. with exercise, particularly with HIIT. This is an important finding because of the predictive value of the VO_2max. for mortality. Only Lewinter, et al. (2015), had studies included with an exercised-based rehabilitation group, the other articles had a comprehensive rehabilitation programme. It can be questioned if the positive effect on VO_2max. is a consequence of the training alone or of the exercise training in combination with other interventions. Since we found an increase of the VO_2max. in all the studies we can conclude that exercise training alone has definitely a positive effect on the exercise capacity.

There has been found a change in systolic and diastolic blood pressure with exercise for different diseases. Oldridge (2012) found a difference between comprehensive rehabilitation and exercise-based rehabilitation. There was no change in blood pressure with exercise-based rehabilitation. In contrast, Taylor, et al. (2004) reported a significant decrease in systolic blood pressure with CR, but did not made a comparison between comprehensive rehabilitation or exercise-based rehabilitation. It is important to note that the study of Oldridge, has a lower methodological quality and there is not done a statistical pooling of the results. There is also a

difference in follow-up, the follow-up in the study of Oldridge was shorter than the follow-up in the study of Taylor, et al. (2004).

On the effect that CR has on HDL, is no consensus. Two studies found no change in HDL (Oldridge, & Taylor, et al., 2004). The methodological quality of Oldridge was lower than that of the other three studies. The follow-up in the study of Oldridge was shorter than the follow-up in the other studies. In the two studies that found a difference, HIIT was applied and compared to CME and a control group.

The LDL will probably not be changed by exercise for patients with CAD, but rather by education or drug therapy. There was nothing mentioned about this outcome for other diseases.

The kind of aerobic exercise programme has no influence on the decrease in triglycerides. Oldridge (2012) found greater improvement in total cholesterol with comprehensive rehabilitation. In contrast, Taylor et al. (2004) did not made a comparison between exercise-based rehabilitation and comprehensive rehabilitation. Taylor, et al. (2006) only examined the effect of exercise-based rehabilitation. Thus, there is still a need for further investigation about the difference between these two forms of rehabilitation to know how much of the effect can be attributed to exercise training.

We can conclude that smoking was reduced in the group of patients which followed an exercise based rehabilitation programme. Nonetheless, with a longer follow-up no significant difference was seen. However, the methodological quality of Taylor, et al. (2006) was poorer than Taylor, et al. (2004). We can conclude with severe caution that longer term interventions should guide and surround patients even more so they do not restart smoking.

There are positive findings on body measures when completing an exercise programme (Hwang, et al., 2011). The type of exercise is not a determining factor according to Hwang, et al. However more research is needed to verify these findings. Future research should investigate if other trainings modalities have different effects on body composition. Also, another CVD should be investigated.

Effects of HIIT and CME on fasting glucose are similar. However, this was only investigated in patients with cardiometabolic disorders. This was only stated by Hwang, et al., more studies are needed to verify these findings. Further research is suggested in patients with another CVD.

5.2.4 Correlation between CV risk factor reduction and prognosis

Taylor, et al. (2004) reported that the reduction in mortality for patients with coronary heart disease is also induced by indirect effects of exercise. This is because exercise improves some of the risk factors. The risk factors that were investigated are blood lipid concentration, blood pressure and smoking. Of these risk factors the total cholesterol levels, triglycerides levels, systolic blood pressure and smoking improved. There was no significant difference in LDL, HDL and diastolic blood pressure between exercise-based rehabilitation and usual care. The missing risk factors in this study are, blood glucose, body measurements and exercise capacity. Taylor, et al. (2006) found greater improvements of some risk factors (cholesterol levels, systolic blood pressure and smoking) in the exercise-based rehabilitation group in comparison with the control group for patients with coronary heart disease. And these risk factors altogether accounted for 58% of the reduction of total mortality. Smoking cessation had the biggest impact on mortality reduction (24%), then cholesterol (19,7%) and blood pressure had the smallest impact (15%). The risk factors that were not examined in this study were blood glucose, body measurements, exercise capacity and there was no specification on blood

lipids. Piepoli, Davos, Francis, and Coats (2004) stated that exercise capacity has a strong connection with survival in patients with heart failure. It would have an even more powerful prognostic value than the risk factors (smoking, blood glucose, blood pressure and cholesterol levels). In the article, Piepoli et al. only investigated the effect of CR on mortality and not on the CV risk factors. Clark, et al. (2005a, 2005b), found a reduction in mortality on longer term follow-up and reported an improvement in cholesterol profile with coronary artery disease. It is possible that there is a connection between these two. However, there was not seen any difference between the three programmes. Thus, if there is a connection, it could well be as a result of the education or counselling and not of exercise training.

5.3 Limitations and strengths

There were several limitations in this study. First, only articles published in English or Dutch were included. Secondly the two reviewers did not each assess all of the studies on methodological quality. However, each of them checked the articles they did not assess for methodological quality. Third, not all of the included articles assessed mortality and CV risk factors, thus it is difficult to make an overall conclusion about the link between these two.

A strength of this study is that multiple CVD's were included and not just one. All of these diseases occur frequently and for all of them is CR is of interest.

5.4 Recommendations

For future research, we suggest a more homogeneous study population. This means an equal distribution in gender and age. Most articles investigated predominantly male and middle-aged patients. Another factor which requires further declaration is the exercise intervention. As of today, many different exercise protocols are used in order to achieve beneficial health benefits. Which one is the most efficient and feasible is unknown. A proper distinction between programmes is recommended. Another striking result is that hospitalization is not different between exercise and control. Is this due to the exercise programme, programme adherence or another factor? Another declaration we should consider for this phenomenon is whether the risk factors reduction gained in the exercise intervention will be reverted after this specific period of time. Further research should asses all the CV risk factors in multiple CVD's with a fixed intervention. The correlation between the change in risk factors and its influence on mortality and morbidity is reported in few studies and these studies only investigated this for CAD. It is thus necessary to investigate this with another CVD.

6 Conclusion

Improvements were seen in CV risk factors with cardiac rehabilitation, as for cardiac-related and all-cause hospitalizations, yet some findings remain unclarified such as the correlation between CV risk factors change and the prognosis, all-cause mortality and morbidity.

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8 Appendices

Table 1: overview of the search strategy

	Keywords web of science	Hits WoK	Hits Pubmed
#1	Cardiovascular diseases (topic)	266754	2135641
#2	Heart diseases (topic)	350207	986769
#3	Vascular diseases (topic)	167111	1465446
#4	Exercise therapy (topic)	31838	37729
#5	Physical therapy (topic)	55857	125673
#6	Rehabilitation (topic)	152408	253796
#7	Cardiovascular risk factors(topic)	126937	163830
#8	Risk factors(topic)	834836	1037420
#9	Prognosis(topic)	288835	1288028
#10	Treatment outcome(topic)	429015	782690
#11	Cardiovascular diseases OR heart diseases OR vascular diseases	68430	35986
#12	Exercise therapy OR physical therapy OR rehabilitation	17542	17681
#13	Cardiovascular risk factors OR risk factors	74843	36883
#14	Prognosis OR treatment outcome	75402	64513
#15	Systematic review OR meta-analysis	209914	/
#16	#11 AND #12 AND #13 AND #14	/	212
#17	#11 AND #12 AND #13 AND #14 AND #15	33	/

With filters on systematic review and meta-analyses, English, human and from 1995.

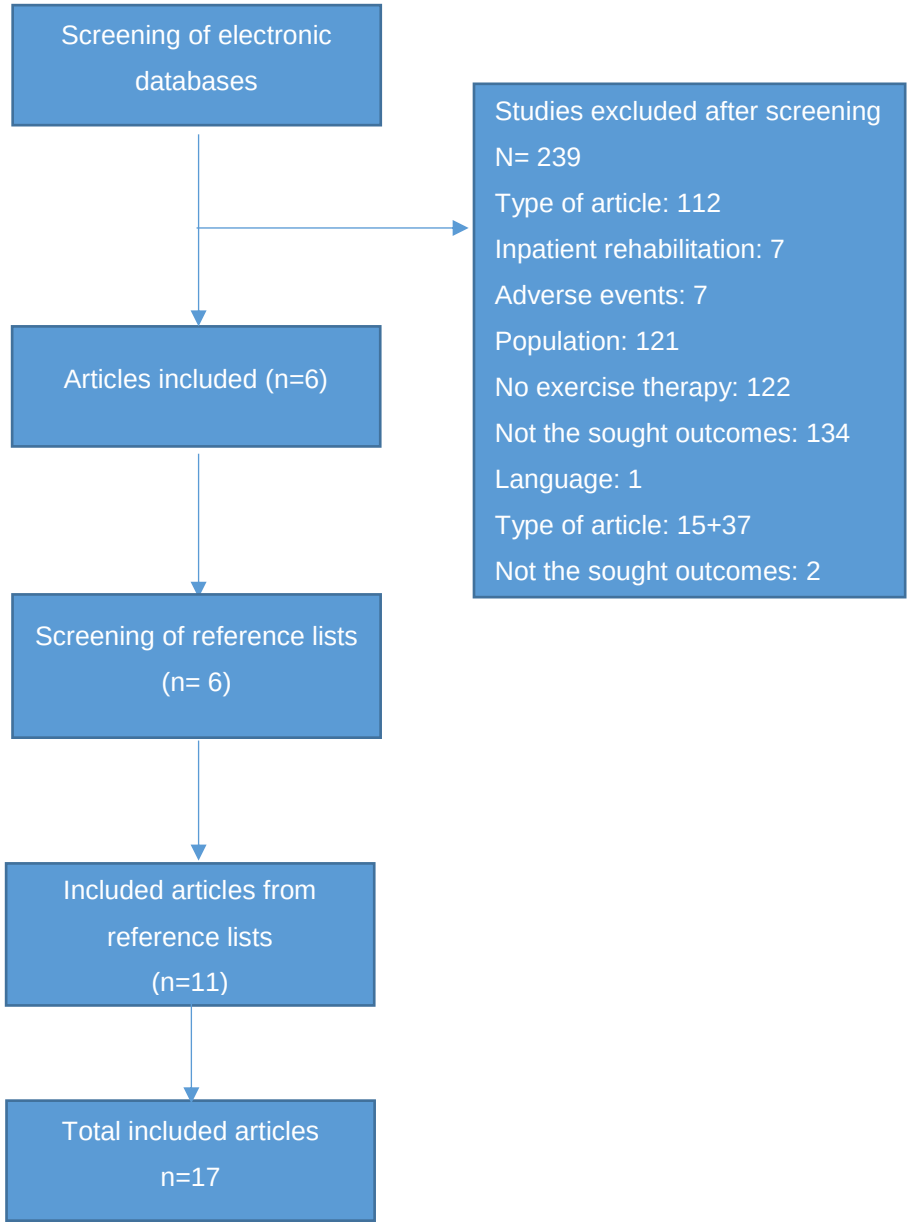

Figure 1: Flow chart search strategy

Table 2: Overview of the excluded studies (n=239)

Reason for exclusion	Number of studies	Author & Year
Type of article	112	Abete, et al. (2013); Akiyode, Thomas, Weaver, and Sahraoui (2013); Alatorre, et al. (2011); Alberti, et al. (2013); Arena, Myers, Forman, Lavie, and Guazzi (2013); Aronow (2006); Asif, and Drezner (2012); Autar (2006); Banerjee, Fowkes, and Rothwell (2011); Barnes (2012); Barua, and O'Hahony (2005); Beauchamp, Peeters, Tonkin, and Turrell (2010); Bisaillon, Kelloway, LeBlanc, Pageau, and Woloshyn (2006); Bugiardini, and Bearey Merz (2005); Caldieraro-Bentley, and Andrews (2013); Carbone, Lavie, and Arena (2017); Castro, Rosillo, Alonso, and Pedersen (2012); Chakravarthy, Joyner, and Booth (2002); Dickens (2015); Chang, Cheng, Richardson, Lee, Starr, and Larson (2011); Cobble, and Frederich (2012); Collins, et al. (2007); Cumberworth, Mabvuure, Hallam, and Hindocha (2013); Czuriga-Kovács, and Brown (2015); Davi, Santilli, and Patrono (2010); Day, (2009); Debus, Ivoghli, Goepfert, Klbel, and Larena-Avellaneda (2011); Del Sindaco, et al. (2007); Dobbels, De Geest, Vanhees, Schepens, Fagard, and Vanhaecke (2002); Dowsley, et al. (2013); Duffy, Phillips, Davis, Donnan, and Vedadhaghi (2003); Erdine, et al. (2006); ESH/ESC Task Force for the Management of Arterial Hypertension (2013); Eves, and Davidson (2011); Featherstone, et al. (2016); Fossum et al. (2007); Galiè, et al. (2009, 2016); Gielen, Sandri, Schuler, and Teupser (2009); Giles, et al. (1996); Graham, et al.(2007); Greving, et al. (2015); Groll, and Fritz (2003); Haffey (2009); Hageman, et al. (2017); Hansen, et al.(2014); Hirsch, Gloviczki, Drooz, Lovell, and Creager (2006); Holland, Navaratnarajah, and Taggart (2016); Holtzman, Caldwell, Walvatne, and Kane (1999); Huckans, Hutson, Twamley, Jak, Kaye, and Storzbach (2013); Hurvitz, Beale, Ried, and Nelson (1999); Husted, et al. (2010); Isaksen, Morken, Munk, and Larsen (2012); Jurgens, et al. (2015); Kerr, Looi, Garofalo, Wells, and McLachlan (2010); Kiernan, Hynes, Ruggiero, Yan, and Jaff (2010); Klomp, Steyerberg, van Urk, Habbema, and Grp (2006); Kornerup, Zwisler, Prescott, and Grp (2011); Kwakkel, Wagenaar, Kollen, and Lankhorst (1996); Lauret, et al. (2012); Lee, et al. (2008); Legato, et al. (2006); Lennon, and Blake (2009); Lewin, and Doherty (2013); Lumsden, Davies, and Peden (2009); Maaijwee, Rutten-Jacobs, Schaapsmeerders, Van Dijk, and De Leeuw (2014); Mancini, et al. (2014); Manna, and Jain (2015); Marciniak, Kaplan, Welty, and Chen (2012); Mehra, et al. (2006); Mezzani, et al. (2013); Moya, Rivas, and Perez-Rondon (2013); Nakajima, et al. (2014); Nicollerat (2000); Novo, et al. (2008); Olin, et al. (2010); Ovbiagele (2010); Pantoni, Poggesi, and Inzitari (2009); Pavy, et al. (2013); Perk, et al. (2012); Pogosova, et al. (2015); Reddy, Dubar, Morgan, and O'Neil (2008); Redon, et al. (2008); Reibis, et al. (2006, 2015); Reis, Holubkov, and Zell (1997); Retrum, et al. (2013); Ruzicka, et al. (2015); Schulman, Beyth, Kearon, and Levine (2008); Schwaab, et al. (2009); Selvan, et al. (2017); Shammas, and Dippel (2005); Sperling, et al. (2015); Spratt (2009); Staessen, et al. (2001); Staimez, Weber, and Gregg (2014); Stemer, Zehetmayer, and Lemmens-Gruber (2009); Thompson, et al. (2003, 2014); Tiessen, Smit, Broer, Groenier, and Van der Meer (2013); Turner, Zhu, and Huynh (2009); van Engen-Verheul, et al. (2012); Van Til, Renzenbrink, Dolan, and Ijzerman (2008); Vanacker, et al. (2017); Verdecchia, Clement, Fagard, Palatini, and Parati (1999); Vernooij, et al. (2012); Verrier, and Malik (2013); Vowden (2001); Wahlgren, et al. (2008); Weinberg, Lau, Rosenfield, and Olin (2011); West, and Jones (2013); Wijeysundera, et al. (2010); Zehr (2011); Zellerhoff, et al. (2009); Zheng, et al. (2014); Zweifel-Zehnder, et al. (2015)
Inpatient rehabilitation	7	Blair, Corrigall, Angus, Thompson, and Leslie(2011); Duffy, Phillips, Davis, Donnan, and Vedadhaghi (2003); Jurgens, et al. (2015); Kerr, Looi, Garofalo, Wells, and McLachlan (2010); Lee, et al. (2008); Meijer, et al. (2004); Stemer, Zehetmayer, and Lemmens-Gruber (2009)

Reason for exclusion	Number of studies	Author & Year
Adverse events of exercise therapy were investigated	7	Asif, and Drezner (2012); Eves, and Davidson (2011); Gommans, et al. (2015); Isaksen, Morken, Munk, and Larsen (2012); Redon, et al. (2008); Thomas, Goodman, and Burr (2011); Zehr (2011)
The population did not meet the criteria	121	Aiello, Cahill, and Wong (2001); Alberts, et al. (2011); Altman, Yu, and Schaefer (2010); Andersen (2017); Asif, and Drezner (2012); Autar, (2006); Avenell, et al. (2004); Barnes, (2012); Barau, and O'Mahony (2005); Bassuk, and Manson (2005); Bauters, and Lemesle (2016); Bugiardini, and Bairey Merz (2005); Caeiro, Ferro, and Costa (2013); Campbell, et al. (2016); Carbone, Lavie, and Arena (2017); Castro, Rosillo, Alonso, and Pedersen (2012); Chakravarthy, Joyner, and Booth (2002); Charlesworth, Foulds, Burr, and Bredin (2011); Chen, et al. (2015); Cobble, and Frederich (2012); Collins, et al. (2007); Corbetta, Sirtori, Castellini, Moja, and Gatti (2015); Cullen, Bayley, Bayona, Hilditch, and Aubut (2007); Cumberworth, Mabvuure, Hallam, and Hindocha (2013); Dal Molin, et al. (2014); Davi, Santilli, and Patrono (2010); Day (2009); Detaille, Heerkens, Engels, van der Gulden, and Van Dijk (2009); Dickens (2015); Dietz, Hoffmann, Lachtermann, and Simon (2012); Duffy, Philips, Davis, Donnan, and Vedadhaghi (2003); Dutton, and Lewis (2015); Erdine, et al. (2006); ESH/ESC Task Force for the Management of Arterial Hypertension (2013) Estes, and Link (2012); Eves, and Davidson (2011); Fagard, et al. (2009); Foley, Salter, and Teasell (2007); Fossum, et al. (2007); Galiè, et al. (2009, 2016); Gellis, and Kang-Yi (2012); Graham, et al. (2007); Groll, and Fritz (2003); Hannawi, Hannawi, Rao, Suarez, and Bershad (2013); Hansen, et al. (2014); Harris, and Hebert (2015); Harrison, Lombard, Moran, and Teede (2011); Hart, and Norman (2006); Hopper, Billah, Skiba, and Krum (2011); Huckans, et al. (2013); Hurvitz, Beale, Ried, and Nelson (1999); Husted, et al. (2010); Isaksen, Morken, Munk, and Larsen (2012), Joris, Zeegers, and Mensink (2015); Keyes, merrick, Frank, Grimm, and Zelefsky (2017); Khan, et al. (2005, 2007); Klom, Steyerberg, van Urk, Habbema, and Grp (2006); Kwakkel, Wagenaar, Kollen, and Lankhorst (1996); Lawler, Filion, and Eisenberg (2011); Lee, Chen, Wu, Wang, Huang, and Piotrkiewicz (2008); Legato, et al. (2006); Lennon, and Blake (2009); Liao, et al. (2016); Lièvre, et al. (2011); Lim, MacFadyen, Clarkson, and Macdonald (1996); Ma, Wang, and Liu (2013); Maaijwee, Rutten-Jacobs, Schaapsmeerders, van Dijk, and De Leeuw (2014); Manna, et al. (2015) Marciniak, Kaplan, Welty, and Chen (2012); McTigue, Hess, and Ziouras (2006); Mehra, et al. (2006); Meijer, et al. (2004); Moteshafi, Zhornitsky, Brunelle, and Stip (2012); Moya, Rivas, and Perez-Rodon (2013); Nakajima, et al. (2014); Nicollerat (2000); Novo, et al. (2008); Ovbiagele (2010); Pang, Charlesworth, Lau, and Chung (2013); Pantoni, Pggesi, and Inzitari (2009); Peel, Thomas, Dittus, Jones, and Lakoski (2014); Perk, et al. (2012); Petersen, Clifton, Lister, and Keogh (2015, 2016); Proietti, et al. (2013); Rajamani, et al. (2013); Reibis, et al. (2015); Reimers, Knapp, and Reimers (2009); Ruzicka, et al. (2015); Schulman, Beyth, Kearon, and Levine (2008); Sadeghi, et al. (2016); Selvan, et al. (2017); Semlitsch, et al. (2013); Skelton, DeMattia, and Flores (2008); Sperling, et al. (2015); Spratt (2009); Staessen, et al. (2001, 1999); Staimez, Weber, and Gregg (2014); Stemer, Zehetmayer, and Lemmens-Gruber (2009); Teleni, et al. (2016); Tiessen, Smit, Broer, Groenier, and Van Der Meer (2013); Tisi, and Than (2014); Turner, Zhu, and Huynh (2009); Uthman, et al. (2015); van Almenkerk, Smalbrugge, Depla, Eefsting, and Hertogh (2015); van Til, Renzenbrink, Dolan, and IJzerman (2008); Vanacker, et al. (2017); Vancampfort, et al. (2012); Veerbeek, Kwakkel, van Wegen, Ket, and Heymans (2011); Verdecchia, Clement, Fagard, Palatini, and Parati (1999); Verrier, and Malik (2013); Vowden (2001); Whalgren, et al. (2008); Wang, and Staessen (2001); Winkes, Hoogeveen, and Scheltinga (2014); Zehr (2011); Zheng, et al. (2014); Zweifel-Zehnder, et al. (2015)

Reason for exclusion	Number of studies	Author & Year
Exercise therapy was not investigated	122	Abu Dabrh, et al. (2015); Akiyode, Thomas, Weaver, and Sahraoui (2013); Alberts, et al. (2011); Aldcroft, Taylor, Blackstock, and O'Halloran (2011); Asif, and Drezner (2012); Autar (2006); Barau, and O'Mahony (2005); Barth, Critchley, and Bengel(2008); Barth, Jacob, Daha, and Critchley (2015); Bauters, and Lemesle (2016); Brown, Clark, Dalal, Welch, and Taylor (2013); Bugiardini, Bairey Merz (2005); Caeiro, L., et al. (2013), Caldieraro-Bentley, Andrews (2013); Campbell, et al. (2016); carbone, Lavie, and Arena (2017); Chang, et al. (2011); Cheng, and Baldwin (2001); Chu, Gotink, Yeh, Goldie, and Hunink (2016); Cobb, Brown, and Davis (2006), Cobble, and Frederich (2012), Collins, et al. (2007); Cornelis, et al. (2015); Cramer, Lauche, Haller, Dobos, and Michalsen (2015); Cullen, Bayley, Bayona, Hilditch, and Aubut (2007); Cumberworth, Mabvuure, Hallam, and Hindocha (2013); Currie, et al. (2015); Czuriga-Kovács, and Brown (2015); Dal Molin, et al. (2014); Davi, Santilli, and Patrono (2010); Detaille, Heerkens, Engels, van der Gulden, and van Dijk (2009); Dickens (2015); Ditewig, Blok, Havers, and van Veenendaal (2010); Dobbels, et al. (2002), Dowsley, et al. (2013); Dutton, and Lewis (2015); Erdine, et al. (2006); ESH/ESC Task Force for the Management of Arterial Hypertension (2013); Estes and Link (2012); Fagard et al. (2009); Featherstone et al. (2016); Fisher, Doree, Mathur, and Martin-Rendon (2015); Flodgren, Rachas, Farmer, Inzitari, and Shepperd (2015); Giles, et al. (1996); Glasser, et al. (2012); Greving, et al. (2015); Hannawi, Hannawi, Rao, Suarez, and Bershad (2013); Hansen, et al. (2014); Harris, and Herbert (2015); Holland, Navaratnarajah, and Taggart (2016); Holtzman, Caldwell, Walvatne, and Kane (1999); Huckans, et al. (2013); Husted, et al. (2010); Janssen, De Gucht, Dusseldorp, and Maes (2013); Jiang, et al. (2016); Joris, Zeegers, and Mensink (2015); Kerr, Looi, Garofalo, Wells, and McLachlan (2010) Kitsios, and Zintzaras (2009); Klomp, Steyerberg, van Urk, Habbema, and Grp (2006); Kwakkel, Wagenaar, Kollen, and Lankhorst (1996); Lee, et al. (2008); Liao, et al. (2016); Lièvre, et al. (2011); Lim, MacFadyen, Clarkson, and Macdonald (1996); Linden, Stossel, and Maurice (1996); Lumsden, Davies, and Peden (2009); Ma, Wang, and Liu (2013); Manna, Jain (2015); Marciniak, Kaplan, Welty, and Chen (2012); McTigue, Hess, and Ziouras (2006); Medvergy, Simonyi, Medvegy, and Pecsvarady (2011); Mehra, et al. (2006); Meijer, et al. (2006); Moran, Teljeur, Harrington, and Ryan (2015); Mookadam, and Arthur (2004); Morling, Maxwell, and Stewart (2013); Moteshafi, Zhornitsky, Brunelle, and Stip (2012); Moulakakis, et al. (2014); Moya, Rivas, and Perez-Rondon (2013); Nakajima, et al. (2014) Pantoni, Poggesi, and Inzitari (2009); Pogosova, et al. (2015); Proietti, et al. (2013); Rajamani, et al. (2013); Redon, et al. (2008); Reibis, et al. (2015); Reid, and Thompson (2013); Reis, and Holubkoc, and Zell (1997); Retrum, et al. (2013); Rosero, Kane, Clagett, and Timaran (2010); Ruzicka, et al. (2015); Schulman, Beyth, Kearon, and Levine (2008); Selvan, et al. (2017); Shammas, and Dippel (2005); Sharples, et al. (2007); Skelton, De Mattia, and Flores (2008); Sperling, et al. (2015); Spratt (2009); Staessen, et al. (2001, 1999); Stewart, Morling, and Maxwell (2016); Tisi, and Than (2014); Touzé, et al. (2013); Tully, and Baumeister (2014); Turner, Zhu, and Huynh (2009); van Almenkerk, Smalbrugge, Depla, Eefsting, and Hertogh (2015); Van Til, Renzenbrink, Dolan, and IJzerman (2008); Veerbeek, Kwakkel, van Wegen, Ket, and Heymans (2011); Verdecchia, Clement, Fagard, Palatini, and Parati (1999); Vernooij, et al. (2012); Verrier, Malik (2013); Vowden (2001); Wahlgren, et al. (2008); Wang, and Staessen (2001); Wang, et al. (2016); Weinberg, Lau, Rosenfield, and Olin (2011); Wijeysundera, et al. (2010); Winkes, Hoogeveen, and Scheltinga (2014); Younge, Gotink, Baena, Roos-Hesselink, and Hunink (2015); Zellerhoff, et al. (2009); Zweifel-Zehnder, et al. (2015)

Reason for exclusion	Number of studies	Author & Year
Not the sought outcomes	134	Abu Dabrh, et al. (2015); Alberti, et al. (2013); Alberts, et al. (2011); Asif, Drezner (2012); Autar (2006); Barnes (2012); Barth, Jacob, Daha, and Critchley (2015); Barua, O'Mahony (2005); Bassuk, and Manson (2005); Bauters, and Lemesle (2016); Burke, Dunbar-Jacob, and Hill (1997); Caeiro, Ferro, and Costa (2013); Caldieraro-Bentley, A.J.,and Andrews (2013), Campbell, et al. (2016), Chang, et al. (2011); Charlesworth, Foulds, Burr, and Bredin (2011); Cheng, Baldwin (2001); Cobble, Frederich (2012); Cornelis, et al. (2015); Cullen, Bayley, Bayona, Hilditch, and Aubut (2007); Currie, et al. (2015); Czuriga-Kovács, Brown (2015); Dal Molin, et al. (2014); Davi, Santilli, and Patrono (2010); Day (2009); Del Sindaco, et al. (2007); Dobbels, et al. (2002); Dowsley, et al. (2013); Duffy, Phillips, Davis, Donnan, and Vedadhaghi (2003); Erdine, et al. (2006), ESH/ESC Task Force for the Management of Arterial Hypertension (2013), Estes and Link (2012); Eves, and Davidson (2011); Featherstone, et al. (2016); Gellis, and Kang-Yi (2012); Glasser, et al. (2012); Gommans, et al. (2015); Greving, et al. (2015); Groll, and Fritz (2003); Guidon, and McGee (2010); Hageman, et al. (2017); Hankey, Norman, and Eikelboom (2006); Hannawi, Hannawi, Rao, Suarez, and Bershad (2013); Hansen, et al.(2014); Harris, and Hebert (2015); Harrison, Lombard, Moran, and Teede (2011); Hart, and Norman (2006); Holland, Navaratnarajah, and Taggart (2016); Huckans, Hutson, Twamley, Jak, Kaye, and Storzbach (2013); Hurvitz, Beale, Ried, and Nelson (1999); Jiang, et al. (2016); Joris, Zeegers, and Mensink (2015); Kerr, Looi, Garofalo, Wells, and McLachlan (2010); King, Humen, and Teo (1999); Kitsios, and Zintzaras (2009); Klomp, Steyerberg, van Urk, Habbema, and Grp (2006); Kornerup, Zwisler, Prescott, and Grp (2011); Kwakkel, Wagenaar, Kollen, and Lankhorst (1996); Lane, Ellis, Watson, and Leng (2014); Lee, et al. (2008); Legato, et al. (2006); Liao, et al. (2016); Lièvre, et al. (2011); Lim, MacFadyen, Clarkson, and Macdonald (1996); Lumsden, Davies, and Peden (2009); Ma, Wang, and Liu (2013); Malgor, et al. (2015); Manna, and Jain (2015); Marciniak, Kaplan, Welty, and Chen (2012); McTigue, Hess, and Ziouras (2006); Medvegy, Simonyi, Medvegy, and Pecsvarady (2011); Mehra, et al. (2006); Meijer, et al. (2004); Moran, Teljeur, Harrington, and Ryan (2015); Morling, Maxwell, and Stewart (2013); Moteshafi, Zhornitsky, Brunelle, and Stip (2012); Moulakakis, et al. (2014); Moya, Rivas, and Perez-Rodon (2013); Nakajima, et al. (2014); Neubeck, et al.(2012); Ovbiagele (2010); Pantoni, Poggesi, and Inzitari (2009); Peel, Thomas, Dittus, Jones, and Lakoski (2014); Petersen, Blanch, Keogh, and Clifton (2015); Petersen, Clifton, Lister, and Keogh (2016); Piepoli, et al. (2016); Proietti, et al. (2013); Rajamani, et al. (2013); Redon, et al. (2008); Reed, Mark, Reid, and Pipe (2013); Reibis, et al. (2006, 2015); Reid, et al. (2013); Reimers, Knapp, and Reimers (2009); Reis, Holubkov, and Zell (1997); Retrum, et al. (2013); Ruzicka, et al. (2015); Schulman, Beyth, Kearon, and Levine (2008); Schwaab, et al. (2009); Selvan, et al. (2017); Shammas, and Dippel (2005); Sharples, et al. (2007); Skelton, DeMattia, and Flores (2008); Sperling, et al.(2015); Spratt (2009), Staessen, et al. (2001, 1999); Staimez, et al. (2014); Stemer, Zehetmayer, and Lemmens-Gruber (2009); Stewart, Morling, Maxwell (2016); Teleni, et al. (2016); Thomas, Goodman, and Burr (2011); Thompson (2014); Tiessen, Smit, Broer, Groenier, and Van der Meer (2013); Tisi, and Than (2014); Touzé, et al. (2013); Tully, and Baumeister (2014); Turner, Zhu, and Huynh (2009); Uddin, et al. (2016); van Almenkerk, Smalbrugge, Depla, Eefsting, and Hertogh (2013); van Engen-Verheul, et al. (2012); Van Til, Renzenbrink, Dolan, and Ijzerman (2008); Vanacker, et al. (2017); Vancampfort, et al. (2012); Veerbeek, Kwakkel, van Wegen, Ket, and Heymans (2011); Verrier, and Malik (2013); Vowden (2001); Wahlgren, et al. (2008); Weinberg, Lau, Rosenfield, and Olin (2011); Winkes, Hoogeveen, and Scheltinga (2014); Zehr (2011); Zellerhoff, et al. (2009); Zweifel-Zehnder, et al. (2015)

Table 3: Quality Assessment of the included articles (n= 17)

Criteria	Clark, AM., et al. 2005a	Clark, AM., et al. 2005b	Cornish, AK., et al. 2010	Davies, EJ., et al. 2010a	Davies; EJ., et al. 2010b	Heran, BS., et al. 2011	Hwang, CL., et al. 2011	Lewinter, C., et al. 2015	Oldridge, N., et al. 2012	Palau, P., et al. 2016	Piepoli, MF., et al. 2004	Sagar VA., et al. 2015	Taylor, RS., et al. 2004	Taylor, RS., et al. 2006	Taylor, RS., et al. 2012	Taylor RS., et al. 2014	Weston, KS., et al. 2014
Formulation of question	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Search	+	+	+	+	+	+	+	+	?	+	+	+	+	?	+	+	+
Selection of articles	+	+	+	+	+	+	+	+	+	+	+	+	+	?	+	+	+
Quality assessment	?	+	?	?	?	+	+	?	-	?	?	+	+	?	+	+	+
Description data-extraction	+	+	?	+	+	+	?	+	+	?	+	+	+	+	+	+	+
Description of most important characteristics	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Statistical pooling	+	+	/	+	+	+	+	+	/	/	+	+	+	+	+	+	/
Clinical and statistical heterogeneity	+	+	-	+	+	+	+	+	?	?	?	+	+	+	+	+	?

+: adequate described; - : inadequate described; ?: not described

Table 4: Strengths and weaknesses (n=17)

Authors, Year	Strengths	Weaknesses
Clark, AM., et al. 2005a	Methodological quality Number of databases searched (7) Compares different types of rehabilitation programs Short and long term follow-up (however, long term is relatively short) Number of included studies (46)	English articles only Methodological quality of the included articles (mean scores 2/5 Jadad) No consistency in the exercise protocols of the included studies
Clark, AM., et al. 2005b	Methodological quality Number of databases searched (6) + bibliographies of identified reviews were checked Number of included articles (63)	English articles only Methodological quality of included articles (mean scores 2/5 Jadad) Heterogeneity amongst participants Relatively short-term follow-up (12 months) Little knowledge of given interventions
Cornisch, AK., et al., 2010	Number of databases searched (7)	English articles only Methodological quality of the included articles Great heterogeneity amongst included reviews No statistical pooling of the data Recruitment bias (only motivated patients) No knowledge of co-therapies Number of included articles (7)
Davies, EJ., et al. 2010a	Methodological quality Number of databases searched (8) No language restrictions Number of included reviews (19)	Relatively short-term follow-up High risk for biases Low quality of included reviews Generalization has to be done with caution, no severe and almost no female patients were included
Davies, EJ., et al. 2010b	Methodological quality An update of previous SR's Number of databases searched (5) + bibliographies of identified reviews were checked Number of included articles (23) No language restrictions	Methodological quality in included articles Relatively short-term follow-up Results not representative for all patients

Authors, Year	Strengths	Weaknesses
Heran, BS., et al. 2011	Methodological quality Number of databases searched (7) Number of included studies (47) Short and long term follow-up (however, long term is relatively short) Examination of the effect of publication before and after 1995 The average age was between 46 and 84 years	The included studies recruited mainly men No consistency in the exercise protocols and setting of the included studies No adequate critical evaluation of the included articles
Hwang, CL., et al. 2011	Methodological quality Number of databases searched (5) The trials included men and women. Good consistency in the exercise protocols of the included studies	Only English articles Number of included studies (6) Methodological quality of the included articles (average 5/10 PEDro) The included trails had a lot of heterogeneity in participant characteristics The study included several diseases, generalization has to be done with caution There is a chance for investigator bias No long term follow-up
Lewinter, C., et al. 2014	Number of databases searched (5) Number of included studies (46) Good consistency in the exercise protocols of the included studies	The included studies recruited mainly men and the average age was 60 years No consistency in the exercise protocols of the included studies English articles only
Oldridge, N., et al. 2012	Number of included studies (21) Compares different types of rehabilitation programs	Methodological quality Only articles since the year 2000 were included Only English articles The included studies recruited mainly men and the average age was ranging from 54.7 to 57.3 years
Palau, P., et al. 2016	No language restrictions	Only 1 database searched Number of included studies (8) No consistency in the exercise protocols of the included studies Heterogeneity in the inclusion criteria of the included studies Short-term follow-up (12-24 weeks) Methodological quality of the included studies was not described Methodological quality was not described Not all the included studies fulfilled the four criteria for defining HFpEF Heterogeneous population

Authors, Year	Strengths	Weaknesses
		The included studies used different measurements to assess functional capacity
Piepoli, MF., et al. 2014	Methodological quality	Number of databases searched (2) Only articles since the year 1990 were included Number of included studies (9) No consistency in the exercise protocols of the included studies
Sagar, VA., et al. 2015	Methodological quality Number of databases searched (8) Number of included studies (33) No language restrictions This review examined if there was a difference in outcome because of publication date Methodological quality of the included articles was moderate Short and long term follow-up (up to 12 months and >12months, however >12 months is relatively short)	Only articles since the year 2008 were included No consistency in the exercise protocols and setting of the included studies The included studies recruited mainly men
Taylor, RS., et al. 2004	Methodological quality Number of databases searched (5) Number of included studies (48) No language restrictions Included reviews must have a follow-up period of at least 6 months This review examined if there was a difference in outcome between studies publicized before 1995 and after 1995	No consistency in the exercise protocols and setting of the included studies Methodological quality of the included articles (average 2/5 Jadad) The included studies recruited mainly men
Taylor, RS., et al. 2006	Patients received only 1 intervention Number of included articles (19)	No direct description of study selection No direct description of included (and excluded) participants No description of control intervention Methodological quality Lack of statistical power Relatively short term follow-up

Authors, Year	Strengths	Weaknesses
Taylor, RS., et al. 2012	Methodological quality Number of databases searched (7) + bibliographies of identified reviews were checked No language restriction	Number of included articles (7, 5 of them reported results of an intervention) Moderate quality of included reviews Short term follow-up Inconsistent outcome and lack of objective criteria to asses HFpEF Heterogeneity amongst participants
Taylor, RS., et al. 2014	Methodological quality No language restrictions Number of databases searched (8) Number of included reviews (33) Methodological quality of the included articles was moderate Short and long-term follow-up (up to 12 months and >12months, however >12 months is relatively short)	Articles since the year 2008 were included The included studies recruited mainly men No consistency in the exercise protocols and setting of the included studies
Weston, KS., et al. 2014	Methodological quality Number of databases searched (4) Gives directions for further investigation Methodological quality of the included articles (average 7,35/10 PEDro)	Number of included studies (10) English articles only Did not objectify a poor lifestyle (= inclusion criteria) No consistency in the protocols of the included studies Different diseases are included in this study, these may have a different response on HIIT

Short term follow-up= <1 year; Relatively short term= <2 years; HFpEF = Heart Failure with preserved Ejection Fraction

Table 5: data-extraction (n=17)

Author & Year	*Population*	*Intervention*	*Mortality*	*Hospitalization*	*Morbidity*	*Exercise capacity*	*Lipids profile*	*Blood pressure*	*Smoking*	*Body measures*	*Glucose*	*Applicability*
Clark, A.M., et al. 2005a	HF with preserved ejection fraction.	education and counselling + supervised exercise program education and counselling + exercise component supervised exercise programs only vs Usual Care	12 months: RR: 0.97 CI: 0.82, 1.14 24 months: RR: 0.53 CI: 0.35, 0.81 at least 5 years: RR: 0.77 CI: 0.63, 0.93									Patients need to come to the centre, but they receive optimal supervision and support on all facets.
Clark, A.M., et al. 2005b	CAD	Comprehensive rehabilitation	All-cause mortality 12 months: RR: 0.97 CI: 0.82, 1.14 24 months: RR: 0.53 CI: 0.31, 0.92 5 years: RR: 0.76 CI: 0.62, 0.92	Up to 12 months: all-cause: RR: 0.84 CI: 0.74, 0.97 CV: RR: 0.76 CI: 0.58, 0.98	Re-infarction at 12 months: RR: 0.80 CI: 0.65, 0.99							Several professionals are needed to guide patients in a comprehensive exercise programme.

Cornisch, AK., et al. 2011	CAD	Interval training vs moderate intensity-continuous	No statistical pooling of the data.		Training can easily be completed in a home-based setting without high costs.
Davies, EJ., et al. 2010a	Systolic heart failure	Exercise training vs usual care	All-cause mortality <12 months: RR: 1.03 CI: 0.70, 1.53. All-cause mortality >12 months: RR: 0.91 CI: 0.78, 1.06.	All hospital admissions <12 months: RR: 0.79 CI: 0.58, 1.07. All hospital admissions >12 months: RR: 0.96 CI: 0.90, 1.02. Heart failure-related hospitalizations <12 months: RR: 0.72 CI:0.52, 0.99.	Intervention does not require special equipment and is feasible and safe in a home-based setting.
Davies, EJ., et al. 2010b	Chronic heart failure	Exercise based intervention vs usual care	All-cause mortality <12 months: RR: 1.02 CI: 0.70, 1.51 All-cause mortality >12 months: OR:	Hospital admissions <12 months: RR: 0.79 CI: 0.58, 1.07 Hospital admissions >12 months: RR:	Exercise intervention has beneficial effects. It does not require special

			0.88 CI: 0.73, 1.07	0.96 CI: 0.90, 1.02 Hospital admission heart failure only: RR: 0.72 CI: 0.52, 0.99							equipment and it is safe.
Heran, BS., et al. 2011	CAD	Exercise training alone or in combination with educational and psychosocial interventions	Total mortality >12 months: RR: 0.87 CI: 0.75, 0.99 CV mortality >12 months: RR: 0.74 CI: 0.63, 0.87	Up to 12 months: RR: 0.69 CI: 0.51, 0.93	Up to 12 months: MI: RR: 0.92 CI: 0.70, 1.22 CABG: RR: 0.91 CI: 0.67, 1.24 PTCA: RR: 1.02 CI: 0.69, 1.50 >12 months: MI: RR: 0.97 CI: 0.82, 1.15 CABG: RR: 0.93 CI: 0.68, 1.27 PTCA: RR: 0.89 CI: 0.66, 1.19						The setting is a supervised outpatient rehabilitation centre. This provides good guidance and motivation.
Hwang, CL., et al. 2011	Cardiometabolic disorders.	Aerobic intensity training vs				VO_2max. MD: 3,60 CI: 2.28, 4.91	HDL (mmol/l):	Systolic (mmHg): WMD: 6.6	Body weight (kg): WMD: -	MD -0,35 CI: -	The training was done on a treadmill

		Continuous moderate training.				WMD: 0.0 CI: -0.1, 0.2 Triglycerides (mmol/l): WMD: -0.2 CI: -0.5, 0.1	CI: -1.9, 15 Diastolic (mmHg): WMD: 2.5 CI: -3.6, 8.6	1.3 CI: -5.8, -3.2 Waist circumference: comparable effect between AIT and CMT. BMI (kg/m^2): WMD: 0.61 CI: -2.1, 3.3	0,87 , 0,16	and cycle ergometer, these can be found in all outpatient rehabilitation settings. AIT is interesting modality for patients who do not like to exercise.
Lewinter, C., et al. 2015	HF	Exercise-based CR	RR: 0.88 CI: 0.77, 1.02	RR: 0,65 CI: 0.50, 0.84	SMD: 0.98 CI: 0.59, 1.37					A comprehensive rehabilitation is possible in a hospital or outpatient clinic or a hospital.
Oldridge, N., et al. 2012	CAD	Exercise training only or comprehensive rehabilitation	No statistical pooling of the data.							Exercise training is possible in every setting. It can be done with or without supervision.

Palau, P., et al. 2016	HF with preserved ejection fraction.	Physical therapy: exercise training and FES	No statistical pooling because of the large amount of heterogeneity (population, interventions, criteria for HFpEF).		The study concluded that physical therapy is safe but there are no data for long-term effects.
Piepoli, MF., et al. 2004	CHF	Exercise training alone vs usual care	All-cause mortality: RR: 0.65 CI: 0.46, 0.92	RR: 0.72 CI: 0.56, 0.93	Everyone benefits from training. Training can be done in a variety of ways.
Sagar VA., et al. 2015	HF with or without preserved ejection fraction.	Exercise-based rehabilitation vs no exercise (active intervention is possible)	Up to 12 months: RR: 0.92 CI: 0.67, 1.26 > 12 months: RR: 0.80 CI: 0.75, 1.02	Up to 12 months: RR: 0.75 CI: 0.62, 0.92 > 12 months: RR: 0.92 CI: 0.66, 1.29 Heart failure specific admission: RR: 0.61 CI: 0.46, 0.80	There is no difference between home based and hospital based rehabilitation, therefore patients can also train at home. Long-term programmes are essential

Taylor, RS., et al. 2004	CAD	Exercise based rehabilitation vs usual care	All-cause mortality: OR: 0.80 CI: 0.68, 0.93 Cardiac mortality: OR: 0.74 CI: 0.61, 0.96	Nonfatal MI: OR: 0.79 CI: 0.59, 1.09 CABG: OR: 0.87 CI: 0.65, 1.06 PTCA: OR: 0.81 CI: 0.49, 1.34	Total cholesterol (mmol/l): WMD: -0.37 CI: -0.63-, 0.11 LDL (mmol/l): WMD: -0.2 CI: -0.53, 0.12 HDL (mmol/l): WMD: -0.05 CI: -0.03, 0.14 Triglycerides (mmol/l): WMD: -0.23 CI: -0.39, -0.07	Systolic (mmHg): WMD: -3.2 CI: -5.4, -0.9 Diastolic (mmHg): WMD: -1.2 CI: -2.7, -0.3	OR: 0.64 CI: 0.50, 0.83	It is not necessary to exercise in a comprehensive program to reduce the risk for mortality. But for the improvements of the cardiac risk factors a comprehensive programme is better.

Taylor, RS., et al. 2006	CAD	Exercise therapy vs usual care	Cardiac mortality at 2 years mean follow-up: RR: 0.72 CI: 0.55, 0.95			Total cholesterol (mmol/l) 2 years mean follow-up: WMD: -0.11 CI: -0.48, 0.26	Systolic blood pressure (mmHg) 2 years mean follow-up: WMD: -1.95 BI: -9.08, 5.18	2 years mean follow-up: RR: 0.82 CI: 0.60, 1.12	Physical therapy is necessary for reducing the risk factors.
Taylor R.S., et al. 2012	HF with preserved ejection fraction.	Exercise training alone, or in a comprehensive rehabilitation vs no exercise training	No deaths	No hospitalization	MD: 3.0 CI: 2.4, 3.6				Patients will need to come to a center to exercise. Optimal guidance and support are offered.
Taylor RS., et al. 2014	HF with or without preserved ejection fraction.	Exercise-based rehabilitation vs no exercise (active	Up to 12 months: RR: 0.93 CI: 0.69, 1.27	Up to 12 months: RR: 0.75 CI: 0.62, 0.92					When patients keep training for more than a year there

		intervention is possible).	> 12 months: RR: 0.88 CI: 0.75, 1.02	> 12 months: RR: 0.92 CI: 0.66, 1.29 Heart failure specific hospital admission: RR: 0.61 CI: 0.46, 0.80		will be reductions of risk of death and hospital admission/ The QOL will improve sooner There are no differences in improvements between home-based and hospital-based rehabilitation for QOL and hospital admissions.
Weston, KS., et al. 2014	Cardiometabolic diseases.	High Intensity Interval training vs Moderate intense continuous training	No statistical pooling for other outcomes.		VO_2 max.(ml/kg/min.): MD 3.03 CI: 2.00, 4.07	These training modalities are possible in any setting.

RR = Relative Risk; OR = Odds Ratio; CI = Claudication Interval; MD = mean difference; WMD = weighted mean difference

SR-RCTs checklist

1 **5.2**

Beoordeling van de kwaliteit van een systematische review van randomised controlled trials (RCT's)

Naam beoordelaar: ..... Datum: .....

Titel: .....

Auteurs: .....

Bron: .....

Korte beschrijving van de onderzochte interventie(s): .....

.....

Korte beschrijving van de controlebehandeling(en): .....

.....

VALIDITEIT

Item	+	–	?
1. Is de vraagstelling adequaat geformuleerd?			
2. Is de zoekactie adequaat uitgevoerd?			
3. Is de selectieprocedure van artikelen adequaat uitgevoerd?			
4. Is de kwaliteitsbeoordeling adequaat uitgevoerd?			
5. Is adequaat beschreven hoe data-extractie heeft plaatsgevonden?			
6. Zijn de belangrijkste kenmerken van de oorspronkelijke onderzoeken beschreven?			
7. Is statistische pooling op een correcte manier uitgevoerd?			
8 Is adequaat omgegaan met klinische en statistische heterogeniteit van de onderzoeken?			

BELANG

Interventie: .....

Controlebehandeling: .....

Neem de desbetreffende waarden over uit de review, indien samenvattende schattingen voorhanden zijn:

Dichotome uitkomsten (genezen / niet-genezen; in leven / overleden)

Uitkomst: .....

Follow-up: ..... weken / maanden / jaren

Aantal onderzoeken: .....

Effectmaat	Waarde	95%-BI	Homogeen?
Relatieve risico (RR)			
Oddsratio (OR)			
Risicoverschil (RV)			

Uitkomst: .....

Follow-up: ..... weken / maanden / jaren

Aantal onderzoeken: .....

Effectmaat	Waarde	95%-BI	Homogeen?
Relatieve risico (RR)			
Oddsratio (OR)			
Risicoverschil (RV)			

Continue uitkomsten (bijvoorbeeld bloeddruk, pijnscore, kwaliteit-van-leven score)

Uitkomst: .....

Follow-up: ..... weken / maanden / jaren

Aantal onderzoeken: .....

Effectmaat	Waarde	95%-BI	Homogeen?
Verschil van gemiddelden (MD)			
Gestandaardiseerd verschil van gemiddelden (SMD)			

Uitkomst: .....

Follow-up: ..... weken / maanden / jaren

Aantal onderzoeken: .....

Effectmaat	Waarde	95%-BI	Homogeen?
Verschil van gemiddelden (MD)			
Gestandaardiseerd verschil van gemiddelden (SMD)			

TOEPASBAARHEID

Toepasbaarheid	Commentaar
1. Overeenkomst van de patiënten in het onderzoek met de eigen patiënt(en)	
2. Haalbaarheid in de eigen praktijkvoering	
3. Voor en nadelen van behandeling voor de patiënt	
4. Verwachtingen, voorkeuren en waarderingen van uw patiënt	

Voortgangsformulier

universiteit hasselt | FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN
www.uhasselt.be/glw
postadres: Universiteit Hasselt | Martelarenlaan 42 | BE-3500 Hasselt
bezoekadres: Universiteit Hasselt | Agoralaan, gebouw D | BE-3590 Diepenbeek
T +32(0)11 26 85 36 | F +32(0)11 26 85 99 | E-mail: glw@uhasselt.be

VOORTGANGSFORMULIER WETENSCHAPPELIJKE STAGE DEEL 1

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
24/10	Zoekstrategie	Promotor: Copromotor: Student(e): Lotte Student(e): Dennis
30/01	Inclusiecriteria + Data-verzameling	Promotor: Copromotor: Student(e): Lotte Student(e): Dennis
6/03	Dataverzameling + kwaliteitsbeoordeling	Promotor: Copromotor: Student(e): Lotte Student(e): Dennis
26/04	Inleiding + resultaten	Promotor: Copromotor: Student(e): Lotte Student(e): Dennis
02/06	Deel 2 : Ethiek & uitkomstmaten Deel 1: Voorzicht	Promotor: Copromotor: Student(e): Lotte Student(e): Dennis
		Promotor: Copromotor: Student(e): Student(e):
		Promotor: Copromotor: Student(e): Student(e):
		Promotor: Copromotor: Student(e): Student(e):
		Promotor: Copromotor: Student(e): Student(e):
		Promotor: Copromotor: Student(e): Student(e):

Logboek Lotte Stassen

datum	*Verrichting*
3/11/16	*1ste afspraak met promotor*
20/12/‘16	*zoekstrategie (PICO opgesteld + zoekstrategie gemaakt Web of science gemaakt, Dennis daarna van Pubmed)*
03/01/‘16	*inclusiecriteria en exclusiecriteria opgesteld*
9/01/17-20/01/17; 2de stagevrije periode	*artikels (selecteren van artikels(lotte en dennis apart)+ reden van exclusie gemaakt (enkel lotte))*
28/01/17-3/02/17; 2de stagevrije periode	*referentielijsten: inclusie gemaakt*
20/01/17-3/02/17 + 2de stagevrije periode+ paasvakantie	*kwaliteitsbeoordeling (14 artikels beoordeeld)*
1ste week paasvakantie	*start schrijven inleiding*
2de week paasvakantie	*tabellen van bijlage+ stroomdiagram (alles gemaakt (lotte): kwaliteitsbeoordeling, exclusie, stroomdiagram, data-extractie, Dennis heeft van zijn artikels erbij gezet)*
1ste week paasvakantie	*methode: Lotte volledig geschreven, enkel Dennis data-extractie(lotte verbetert)*
9/05/17, 3u	*tabellen aanpassen*
20/05/17 11u-12u45 en 13u15-14u15 + 16u-17u	*sterkte-zwakte + resultaten (Lotte 12 van de 17 artikels)*
21/05/17 8u-10u + 13u-17u	*resultaten schrijven*
22/05/17 8u30-9u30 + 13u-17u	*resultaten schrijven*
25/05/17 11u30-12u30+ 13u30-19u30	*discussie schrijven: reflectie kwaliteit studies, reflectie bevindingen.*
25/05/17 20u-20u30	*start deel 2: protocol, schrijven van methoden en interventie*
26/05/17 10u-12u + 13u30-14u30	*schrijven discussie (bevindingen en sterktes en zwaktes + verdere aanbevelingen de dingen die uitgeschreven moeten worden)*
26/05/17 19u30-22u30	*referentielijsten maken (exclusie en deel inclusie)*
27/05/17 8u30-10u30 + 14u30-17u30 17u30-18u30	*discussie schrijven (link + sterkte en zwaktes)*
27/05/17 18u30-19u00	*referentielijst (op juiste volgorde)*
27/05/17 19u30-20u30	*outline schrijven*
28/05/17 11u15-15u30	*voorpagina (alles behalve 1 puntje) + referentielijst afwerken*
29/05/17 10u-12u00 en 18u-21u00	*tabellen exclusie aanpassen*

29/05/17	*Mail sturen naar professor Hansen (nalezen tekst + ondertekenen inschrijvingsformulier)*
30/05/17 18u30-21u30	*exclusie referentielijsten, maken.*
1/06/17 16u-20u	*aanpassen referenties in tekst*
3/06/17 10u-12u; 16u-19u30	*Verbetering tekst + deel 2 uitkomstmaten en interventie schrijven*
4/06/17 9u30-12u00 *12u40-13u; 15u30-17u; 18u-20u30*	*Validiteit en betrouwbaarheid meetinstrumenten (BMI, balance scale, CPET, blood sampling)*
5/06/17 7u30-8u	*Validiteit en betrouwbaarheid meetinstrumenten (afwerken)*
8/06/17 15u30-18u00	*Nalezen abstract en deel resultaten+discussie* *Mail sturen naar Hansen, code van medische commissie + vragen hoe de criteria onafhankelijkheid voldaan is*
10/06/17 8u45-12u, 14u-17u, 19u-20u30	*exclusie tabel*
11/06/17 11u30-12u30 13u30-16u30	*exclusie tabel*

Logboek Dennis Snoekx

Datum	Verrichting
18/10/2016	Aanvraag afspraak tot ondertekenen masterproefcontract
24/10/2016	Ondertekenen masterproefcontract
14/11/2016	Eerste gesprek promotor. Richtlijnen ontvangen voor opstart literatuursearch
08/01/2017	Opzoeken Keywords
12/01/2017	Aanpassen keywords
25/01/2017	Afspraak Hanssen verdere stappen iv literatuurselectie
30/01/2017	Afspraak Hanssen data set
14/02/2017	Selecteren artikels PubMed
26/02/2017	Selecteren artikels Web of Science
27/03/2017	Selecteren extra artikels uit referentielijst
03/04/2017	Selecteren extra artikels uit referentielijst
11/04/2017	Kwaliteitsbeoordeling artikels
15/04/2017	Kwaliteitsbeoordeling artikels
17/04/2017	Kwaliteitsbeoordeling artikels
20/04/2017	Kwaliteitsbeoordeling artikels
26/04/2017	Afspraak D. Hansen
27/04/2017	Schrijven discussie
01/05/2017	Schrijven inleiding
04/05/2017	Herschrijven discussie + referentielijst aanvullen
08/05/2017	Sterktes + zwaktes artikels
09/05/2017	Sterktes + zwaktes artikels
10/05/2017	Aanvullen kwaliteitstabel
11/05/2017	Aanvullen resultatentabel
13/05/2017	Herschrijven inleiding
15/05/2017	Finaal afwerken inleiding + doorsturen naar promotor
22/05/2017	Finaal afwerken tabel sterkte + zwakte artikels
23/05/2017	Finaal afwerken resultaten tabel
26/05/2017	Schrijven resultaten
29/05/2017	Schrijven discussie
01/06/2017	Schrijven discussie
05/06/2017	Schrijven abstract
06/06/2017	Herschrijven verbeteringen Lotte
07/06/2017	Opmaak afwerken
10/06/2017	Finaal controleren +

PART II: RESEARCH PROTOCOL

1 Introduction

CVD's are a major problem these days. The prevalence is increasing because of the lifestyle (high blood pressure, less exercise, smoking behaviour, eating food with too much fat and/or sugar, drinking too much soda) we lead. These diseases entail a higher risk for mortality and morbidity. To reduce this risk, patients are referred to CR. Patients exercise to reduce their CV risk factors and enhance their physical fitness. From our literature study, we concluded that CR has a positive influence on the VO_2max., systolic blood pressure, triglycerides and total cholesterol. Two studies also reported a positive influence of smoking, systolic blood pressure, triglycerides and total cholesterol on mortality reduction. These studies did not take blood glucose, VO_2max. or body measurements into account. Thus, to exercise efficiently it is necessary to know if these CV risk factors have an influence on mortality as well. Also important is the correlation of all these CV risk factors and morbidity. It is important to know which change in CV risk factors have an influence on the prognosis, because it is then possible to exercise more focused. And we know then, that the approach for the CV risk factors that are not changed or have no positive influence on the prognosis, needs to change.

2 Aim of the investigation

2.1 Investigation question

Which of the improvements in CV risk profile and physical fitness, induced by CR, are related to a better prognosis in persons with a CV disease?

2.2 Hypotheses

We will expect that all the CV risk factors and the exercise capacity will change positively and have a correlation with the mortality and morbidity. And this for both coronary artery diseases and chronic heart failure.

3 Methods

3.1 Study design

The study will be an observational, prospective cohort study. We will extract and analyse the data of patients who rehabilitated at ReGo.

3.2 Subjects

All the patients with chronic heart failure or coronary artery disease who are referred for rehabilitation ReGo (rehabilitation and health centre) of the 'Jessa' hospital.

3.2.1 Inclusion criteria

- Coronary artery diseases
- Chronic heart failure: systolic and diastolic

3.2.2 Exclusion criteria

- Comorbidities: respiratory conditions such as COPD and asthma, kidney diseases, cancer, neurological conditions
- Peripheral artery disease
- Cardiomyopathy
- Congenital conditions
- Patients with a pacemaker
- Hospitalized patients: patients with an acute exacerbation or event

3.3 Medical ethics

This study is approved by the medical committee (B24301629466). All the patients signed an informed written consent.

3.4 Intervention

Data will be extracted and analysed from patients who have done an exercise programme of twelve weeks at ReGo. All of them will have an individualized programme with aerobic and resistance training. These patients have undergone a cardiopulmonary exercise test (CPET) before, during and after their rehabilitation. The CPET measures exercise capacity. Patients will perform the test on a cycle ergometer, the load will increase progressive (for example 10 Watt increase per minute). An average test duration is eight to twelve minutes. During this test, several outcomes will be measured. The ventilation, VO_2 and VCO_2 will be measured to determine the VO_2max., ECG-monitoring will be done during the test to measure the heartrate and possible cardiac arrhythmias, oxygen saturation and blood pressure will be measured several times during the test and blood lactate will be measured. Based on the results of this test, a personalised exercise programme can be prepared. The blood lipids, blood glucose concentration will be measured via blood sampling. Body measurements will be measured using a balance scale for body weight, and a length meter will be used to

measure the body length. The blood pressure will also be measured frequently, using a sphygmomanometer. The change in smoking and medication intake will be noted. There is already an excel-file with data from 2013, 2014, 2015 and 2016 made up (see figure 1).

3.5 Outcomes

3.5.1 Primary outcomes

Change in CV risk factors:

- Blood glucose concentration
- Blood lipid concentration: LDL, HDL, triglycerides and total cholesterol
- VO_2max.
- Blood pressure: systolic and diastolic
- Body measurements: length, weight and BMI
- Smoking

Prognosis:

- Mortality
- Morbidity: angina pectoris, acute myocardial infarction, resuscitation, revascularisation, pacemaker, myocardial ischemia

For the mortality and morbidity there is a follow-up period of two years.

3.5.2 Secondary outcomes

- Age
- Sex
- Medication use (possible confounder): angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, statins, beta-blockers, fibrates, calcium-antagonists, diuretics, anti-coagulations, niacin, nitrates, metformin's, sulfonylurea, meglitinide, alfa glucosidase inhibitors, DPP4-inhibitors, incretins and insulin analogue.

The scale level for all the outcomes is ratio, except for the scale level of smoking, mortality and morbidity, sex and medication use which is nominal.

3.5.3 Validity and reliability outcome measures

3.5.3.1 CPET

There are no studies that examine the validity of the CPET, this is probably because the CPET is seen as the golden standard for measuring the VO_2max. There are several studies that report on reliability of the CPET for patients with heart failure. These studies concluded that the CPET has a good reliability. There are no studies that report on reliability for patients with coronary artery diseases.

In the study of Scott, et al. (2012) fifty-two patients with HF did the CPET twice, with an interval of three weeks. The reliability of the variables was excellent. There was no significant within-subject variability as to the VO_2max. and ventilatory, anaerobic threshold. It is not necessary to execute this test multiple times. This is because the test is not subject to learning effect or placebo effect. The intra-observer reliability is good.

The correlation coefficients and intraclass correlations:

	Correlation coefficient	**p-value**	**Interclass correlations**
VO_2	r= 0,85	p<0,001	ICC= 0,855
Ventilatory, anaerobic threshold	r= 0,79	p<0,001	ICC= 0,790
VE/VCO_2 slope	r= 0,87	p<0,001	ICC= 0,864
HR	r= 0,94	p<0,001	ICC= 0, 938

Barron et al. (2014) investigated the reliability of the CPET for multiple diseases including HF. The influence of the different diseases and characteristics of the patients on the reliability was also measured.

Most of the variables had an excellent reliability. There was little influence of age, sex, BMI, test protocol, test duration and diseases on the reliability. It is not necessary to do multiple tests in order to enhance the test retest reliability.

Table 2. Test–retest reliability measurements of the full cohort

	Overall mean (tests 1 and 2)	MD (95% limits of agreement)	SDD	CoV	ICC (95% CI)
Peak VO_2	1314.2	24 (−200.2, 248.3)	114.4	0.09	0.95 (0.94, 0.97)
Peak VO_2/kg	17.07	0.35 (−2.52, 3.22)	1.46	0.09	0.94 (0.92, 0.96)
% Predicted peak VO_2	73.1	1.6 (−10.7, 13.9)	6.3	0.09	0.93 (0.89, 0.95)
AT	938.1	47.4 (−194.9, 289.8)	123.6	0.13	0.84 (0.78, 0.89)
AT (% of predicted peak VO_2)	52.3	2.8 (−9.7, 15.3)	6.4	0.12	0.86 (0.79, 0.90)
OUES	1.65	0.01 (−0.41, 0.43)	0.21	0.13	0.93 (0.90, 0.95)
OUES 25–75	1.64	0.06 (−0.64, 0.75)	0.35	0.22	0.76 (0.63, 0.86)
OUES 50	1.58	0.04 (−0.63, 0.72)	0.34	0.22	0.79 (0.71, 0.86)
OUES 70	1.66	0.04 (−0.6, 0.69)	0.33	0.20	0.81 (0.71, 0.88)
OUES 90	1.67	0.01 (−0.54, 0.57)	0.28	0.17	0.87 (0.79, 0.92)
OUEP	33.2	0.23 (−3.99, 4.45)	2.2	0.06	0.91 (0.87, 0.94)
O_2 pulse	10.95	0.01 (−1.68, 1.7)	0.86	0.08	0.96 (0.94, 0.97)
VE/VCO_2 slope 1	35.1	0.34 (−7.47, 8.15)	4.0	0.11	0.88 (0.79, 0.93)
VE/VCO_2 slope 2	37.2	0.58 (−7.87, 9.02)	4.3	0.12	0.88 (0.81, 0.93)
VE/VCO_2 ratio nadir	33.6	0.42 (−3.61, 4.44)	2.1	0.06	0.92 (0.89, 0.95)
VE/VCO_2 ratio at AT	35.7	0.35 (−6.25, 6.94)	3.4	0.09	0.84 (0.71, 0.92)
VE/VCO_2 ratio at VCP	35.7	0.3 (−11.18, 11.78)	5.9	0.16	0.93 (0.81, 0.98)
RER at rest	0.79	−0.01 (−0.15, 0.14)	0.07	0.09	0.25 (0.03, 0.45)
RER at AT	0.87	−0.01 (−0.11, 0.1)	0.05	0.06	0.49 (0.28, 0.65)
RER at peak	1.09	0 (−0.13, 0.14)	0.07	0.06	0.82 (0.74, 0.88)
$p_{ET}CO_2$ at AT	35.6	−0.63 (−5.27, 4.01)	2.4	0.07	0.83 (0.74, 0.89)
HR at rest	938.1	1.65 (−14.03, 17.32)	8.0	0.10	0.83 (0.74, 0.89)
HR at peak	122.6	3.54 (−16.55, 23.63)	10.2	0.08	0.91 (0.86, 0.94)
Double product	20194	671 (−4987, 6328)	2887	0.14	0.90 (0.83, 0.94)
Peak circulatory power	216409	4823 (−55098, 64743)	30572	0.14	0.93 (0.90, 0.96)
O_2 saturations at rest	97.7	0.15 (−3.79, 4.09)	2.0	0.02	0.60 (0.31, 0.79)
O_2 saturations at peak	96.5	0.09 (−3.9, 4.08)	2.0	0.02	0.80 (0.64, 0.89)
Breathing reserve at AT	64.4	−1.5 (−19.4, 15.55)	5.7	0.09	0.93 (0.87, 0.96)
Breathing reserve at peak	32.0	−1.92 (−7.64, 11.02)	8.9	0.28	0.92 (0.86, 0.95)
Rf at peak	35.4	1.69 (−7.64, 11.02)	4.8	0.13	0.76 (0.58, 0.87)
VE at peak	54.8	2 (−13.29, 17.28)	7.8	0.14	0.89 (0.83, 0.94)
VO_2/WR relationship	8.67	0.23 (−2.65, 3.11)	1.5	0.17	0.70 (0.51, 0.82)
Peak work rate	92.2	5.08 (−12.12, 22.27)	8.8	0.10	0.95 (0.93, 0.97)
HR/VO_2 slope	0.05	0.002 (−0.029, 0.033)	0.0	0.29	0.87 (0.74, 0.93)
HR/VO_2 intercept	54.61	0.07 (−24.44, 24.58)	12.5	0.23	0.79 (0.70, 0.86)

The study of Marburger, Brubaker, Pollock, Morgan, and Kitzman (1998) investigated the reliability of the CPET for older adults with HF. The reliability for the ventilatory, anaerobic threshold is greater with the Wasserman method than with the V-slope method (ICC: 0,71 en 0,65). The correlation of the VO_2 and the VAT was high for both methods (r= 0,92).

De interclass correlation coefficients and coefficients of variations:

	Coefficients of variations	**Interclass correlations**
VO_2max.	CV= 6,1	ICC= 0,91
Duration test	CV= 5,2	ICC= 0,92
Ventilatory, anaerobic threshold, Wasserman	CV= 8,9	ICC= 0,71
VAT, V-slope	CV=10,2	ICC= 0,65
HR max.	CV= 4,4	ICC= 0, 87
RER max.	CV= 4,8	ICC= 0,63

3.5.3.2 Weighing scale

There was only one article found on the reliability and validity of weighing scales. This article investigates this in the general population and not for HF or CAD.

Yorkin, Spaccarotella, Martin-Biggers, Quick, and Byrd-Bredbenner (2013) investigated the reliability and validity of weighing scales in the general population. The test retest reliability was good, all scales measured the same weights for different loads on the two tests. Although the dial scales measured significantly different on the two tests when a 75kg calibration weight was applied. The dial scales were significantly more imprecise than the digital scales. With increasing weight load the scales became more imprecise. There was no difference for the age of the scale, thus the age of the scale has no influence on the increasing imprecision. Rather the type of scale is a factor for the increasing imprecision. The overall reliability and validity of weighing scales, especially digital scales, is good.

3.5.3.3 BMI

In the study of Romero-Corral (2008) the validity and reliability of the BMI was measured in an adult population. There was no exclusion of cardiovascular diseases. In this study, there was a strict protocol for measuring body weight and height. There was a good correlation between BMI and body fat percentage (BF%) (r= 0.65) and lean mass for men (r= 0.73). There was an excellent correlation of the BMI with BF% (r= 0.87) and a good correlation with lean mass in women (r= 0.74). BMI had a better correlation with BF% than with lean mass in women. In men aged between 20 and 49,9 years there was a better correlation with lean mass, in older men there was no difference between the correlations.

Table 3 Comparisons of race-adjusted correlation coefficients between BMI and BF % with BMI and lean mass by sex and age groups

Age group (n)	*BMI—BF% Adjusted ρ*	*BMI—lean mass (kg) Adjusted ρ*	*Correlation comparisons P-value*
Men (6580)	0.65*[a]	0.73*[a]	<0.0001
20–29.9 (1514)	0.69*	0.71*	0.038
30–39.9 (1353)	0.66*	0.70*	0.061
40–49.9 (1120)	0.67*	0.72*	0.077
50–59.9 (773)	0.62*	0.76*	0.142
60–69.9 (1026)	0.60*	0.73*	0.111
70–79.9 (700)	0.60*	0.73*	0.188
Women (7021)	0.87*[a]	0.74*[a]	<0.0001
20–29.9 (1487)	0.89*	0.70*	0.006
30–39.9 (1589)	0.90*	0.74*	0.003
40–49.9 (1204)	0.85*	0.77*	0.015
50–59.9 (884)	0.86*	0.77*	0.035
60–69.9 (995)	0.84*	0.72*	0.039
70–79.9 (779)	0.82*	0.69*	0.086

Abbreviations: BF, body fat; BMI, body mass index. **P*-value <0.0001.
[a]Additionally adjusted for age.

3.5.3.4 Blood sampling

No results

3.5.3.5 Blood pressure

The central systolic blood pressure measured via non-invasive techniques was significantly (P<0.001) and strongly correlated with the invasive technique measured at the ascending aortic artery (ICC: 0.91 and 0.90). This was for the SphygmoCor and Omron devices. However, both devices underestimated the central systolic blood pressure significantly with an average difference of -15 mmHg (95% CI: -17, -13 mmHg) and -2 mmHg (95% CI: -4, 0 mmHg). The diastolic blood pressure was also significantly (P<0.001) and strongly correlated with the invasive technique (ICC: 0.74 and 0.91).

The oscillometric measured blood pressure of the a. Brachialis was significantly and strongly correlated with the invasive method (ICC 0.89, 0.84 and 0.87 for systolic, diastolic and pulse pressure). Again, there is an underestimation with the non-invasive techniques.

3.6 Data-analysis

We will use logistic, multivariate regression. Our dependent variables are, mortality and morbidity. Our independent variables are; blood glucose concentration, blood lipid concentration (LDL, HDL, triglycerides, and total cholesterol), VO_2max., blood pressure (systolic and diastolic), body measurements (length, weight and BMI), smoking, age, sex and medication use.

The significance level will be set on $p < 0,05$. We will use JMP pro to do our statistical analysis.

4 Time planning

- Data-extraction: from July 2017 to March 2018
- Writing Introduction and methods: From September to December 2017
- Data-analysis: March 2018
- Writing results, discussion, conclusion and abstract: May 2018

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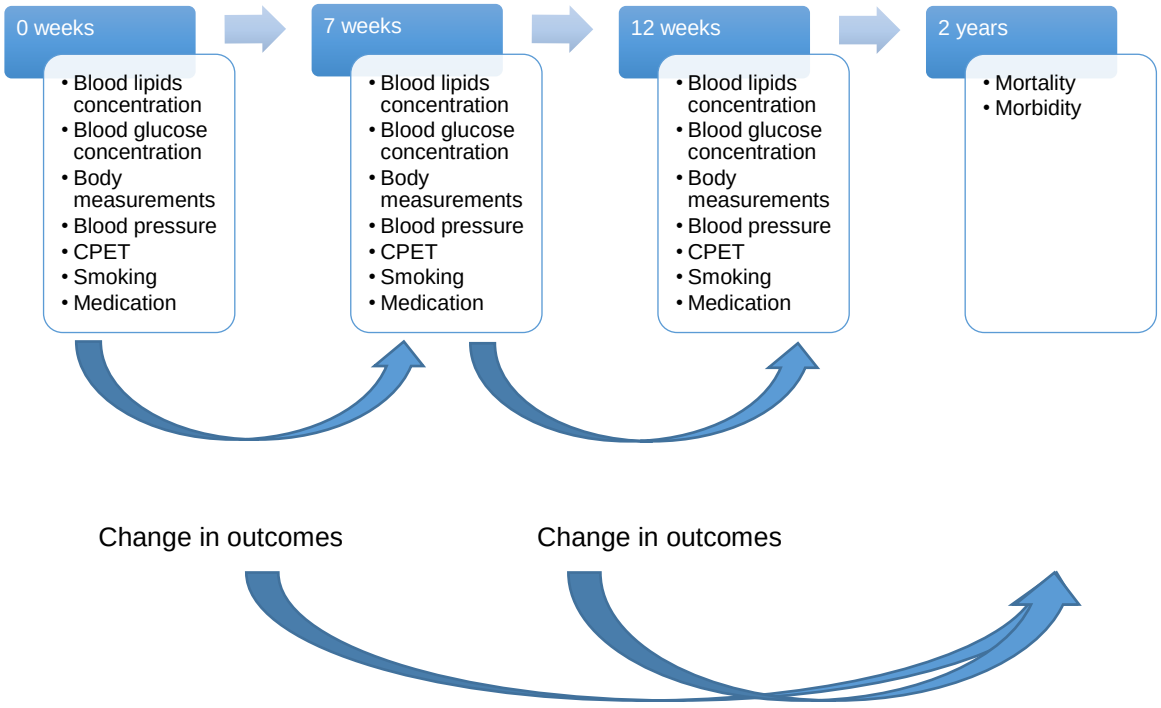
6 Appendices protocol



Correlation between CV risk factors, physical fitness and prognosis

Figure 2: Research protocol

Informed written consent

Titel van de studie: Invloed van trainingsmodaliteiten op kwaliteit van leven in hartpatienten tijdens revalidatie

Opdrachtgever van de studie: *Jessa ziekenhuis, Stadsomvaart 11, 3500 Hasselt*

Onderzoeksinstelling: Universiteit Haselt, REVAL/BIOMED, Agoralaan Gebouw A, 3590 Diepenbeek

Ethisch comité: *Jessa ziekenhuis, Hasselt*

Plaatselijke artsen-onderzoekers: *Prof. dr. Dominique Hansen, dominique.hansen@uhasselt.be*

I Noodzakelijke informatie voor uw beslissing om deel te nemen (4 pagina's)

Inleiding

U wordt uitgenodigd om deel te nemen aan een observationele klinische studie. Dit betekent dat de behandeling die u werd voorgesteld op de gebruikelijke manier werd voorgeschreven, in overeenstemming met de voorwaarden voor goede medische praktijk en onafhankelijk van uw eventuele deelname aan deze studie. Wij vragen u alleen om gegevens uit uw medisch dossier te mogen verzamelen zodat we ze kunnen combineren met de gegevens van andere patiënten die dezelfde behandeling krijgen en zodat we ze voor onderzoeksdoeleinden statistisch kunnen verwerken. Wij zullen u geen enkele andere procedure voor diagnose of opvolging voorstellen, behalve enkele vragenlijsten die u zal moeten invullen.

Voordat u akkoord gaat om aan deze studie deel te nemen, vragen wij u om kennis te nemen van wat deze studie zal inhouden op het gebied van organisatie, zodat u een welbewuste beslissing kunt nemen. Dit wordt een "geïnformeerde toestemming" genoemd.

Wij vragen u de volgende pagina's met informatie aandachtig te lezen. Hebt u vragen, dan kan u terecht bij de arts-onderzoeker of zijn of haar vertegenwoordiger.

Dit document bestaat uit 3 delen: essentiële informatie die u nodig heeft voor het nemen van uw beslissing, uw schriftelijke toestemming en bijlagen waarin u meer details terugvindt over bepaalde onderdelen van de basisinformatie.

Als u aan deze studie deelneemt, moet u weten dat:

- De behandeling die de arts-onderzoeker u in overeenstemming met de huidige aanbevelingen heeft voorgesteld niet zal veranderen door uw deelname aan deze studie.
- Deze klinische studie opgesteld is na evaluatie door één of meerdere ethische comités.
- Uw deelname is vrijwillig; er kan op geen enkele manier sprake zijn van dwang. Voor deelname is uw ondertekende toestemming nodig. Ook nadat u hebt getekend, kan u de arts-onderzoeker laten weten dat u uw deelname wilt stopzetten.
- De gegevens die in het kader van uw deelname worden verzameld, zijn vertrouwelijk. Bij de publicatie van de resultaten is uw anonimiteit verzekerd.
- Er is een verzekering afgesloten voor het geval dat u schade zou oplopen in het kader van uw deelname aan deze klinische studie.
- Indien u extra informatie wenst, kan u altijd contact opnemen met de arts-onderzoeker of een medewerker van zijn of haar team.

Aanvullende informatie over uw "Rechten als deelnemer aan een klinische studie" vindt u in de bijlage.

Doelstellingen en verloop van de studie

Deze klinische studie is georganiseerd om vast te stellen wat het effect is van revalidatie, en verschillende revalidatievormen, op kwaliteit van leven in personen met coronair vaatlijden en/of hartfalen.

Wij stellen u voor om aan deze klinische studie deel te nemen omdat uw arts u hartrevalidatie heeft voorgesteld in het kader van uw klinische situatie.

Aan deze klinische studie zouden 1000 patiënten moeten deelnemen, allen in België.

Om aan deze studie te kunnen deelnemen, moet u een kransslagaderaandoeining en/of hartfalen hebben, en bereid zijn een 12-weken durend revalidatieprogramma in het ReGo van Jessa ziekenhuis te volgen.

De duur van uw deelname aan deze studie bestaat enkel uit 3 routineraadplegingen tijdens dewelke uw arts-onderzoeker u zal vragen om alle voor de studie noodzakelijke gegevens en informatie te verzamelen - zoals uw demografische gegevens (leeftijd, gewicht, lengte, geslacht) evenals gegevens over uw medische voorgeschiedenis, uw geneesmiddelengebruik, uw fysieke fitheid, en cardiovasculair risicoprofiel.

Uw arts-onderzoeker zal u ook vragen om 2 vragenlijsten in te vullen die de kwaliteit van leven en angst/depressiegevoelens evalueren.

Het invullen van deze vragenlijsten zal ongeveer 10 minuten van uw tijd in beslag nemen tijdens elke raadpleging.

Beschrijving van de risico's en van de voordelen

Zoals hierboven vermeld, stemmen de behandeling die u werd voorgesteld en de procedures voor diagnose en opvolging overeen met de goede medische praktijken. Uw deelname aan deze studie houdt geen enkel gezondheidsrisico in.

Ook moet u niet verwachten dat uw deelname aan deze studie u persoonlijke voordelen zal opleveren. U moet begrijpen dat uw deelname aan deze studie ervoor zal zorgen dat wij beter zullen begrijpen wat de impact van hartrevalidatie op kwaliteit van leven is, en bijgevolg in de toekomst betere behandelingen kunnen voorstellen.

Intrekking van uw toestemming

U neemt vrijwillig deel aan deze studie en u hebt het recht om uw toestemming voor gelijk welke reden in te trekken. U hoeft hiervoor geen reden op te geven.

Als u uw toestemming intrekt, zullen de gegevens bewaard blijven die tot op het ogenblik van uw stopzetting werden verzameld. Dit om de geldigheid van de studie te garanderen. Er zal geen enkel nieuw gegeven aan de opdrachtgever worden gegeven.

Als u aan deze studie deelneemt, vragen wij om:

- Tenvolle mee te werken voor een correct verloop van de studie.
- Geen informatie over uw gezondheidstoestand, de geneesmiddelen die u gebruikt of de symptomen die u ervaart te verzwijgen.
- Uw arts-onderzoeker op de hoogte te brengen als men u voorstelt om aan een andere studie deel te nemen zodat u met hem/haar kan bespreken of u aan deze studie kunt deelnemen en of uw deelname aan de huidige klinische studie moet worden stopgezet.

6.1.1 Contact

Als u bijkomende informatie wenst, maar ook ingeval van problemen of als u zich zorgen maakt, kan u contact opnemen met de arts-onderzoeker (prof. dr. Dominique Hansen) op het telefoonnummer 0497 875866.

Als u vragen hebt met betrekking tot uw rechten als deelnemer aan de studie, kan u contact opnemen met de ombudsdienst in uw ziekenhuis op het telefoonnummer: 011 33 54 90. Indien nodig kan de ombudsdienst u in contact brengen met het Ethisch Comité.

Titel van de studie: Invloed van trainingsmodaliteiten op kwaliteit van leven in hartpatienten tijdens revalidatie

II Geïnformeerde toestemming

Deelnemer

Ik verklaar dat ik geïnformeerd ben over de aard, het doel, de duur, de eventuele voordelen en risico's van de studie en dat ik weet wat van mij wordt verwacht. Ik heb kennis genomen van het informatiedocument en de bijlagen ervan.

Ik heb voldoende tijd gehad om na te denken en met een door mij gekozen persoon, zoals mijn huisarts of een familielid, te praten.

Ik heb alle vragen kunnen stellen die bij me opkwamen en ik heb een duidelijk antwoord gekregen op mijn vragen.

Ik begrijp dat mijn deelname aan deze studie vrijwillig is en dat ik vrij ben mijn deelname aan deze studie stop te zetten zonder dat dit mijn relatie schaadt met het therapeutisch team dat instaat voor mijn gezondheid.

Ik begrijp dat er tijdens mijn deelname aan deze studie gegevens over mij zullen worden verzameld en dat de arts-onderzoeker en de opdrachtgever de vertrouwelijkheid van deze gegevens verzekeren overeenkomstig de Belgische wetgeving ter zake.

Ik stem in met de verwerking van mijn persoonlijke gegevens volgens de modaliteiten die zijn beschreven in de rubriek over het verzekeren van de vertrouwelijkheid (bijlage). Ik geef ook toestemming voor de overdracht naar en verwerking van mijn gecodeerde gegevens in andere landen dan België.

Ik heb een exemplaar ontvangen van de informatie aan de deelnemer en de geïnformeerde toestemming.

Naam, voornaam, datum en handtekening van de deelnemer

Arts-onderzoeker

Ik ondergetekende prof. dr. Dominique Hansen, arts-onderzoeker, verklaar de benodigde informatie inzake deze studie mondeling te hebben verstrekt evenals een exemplaar van het informatiedocument aan de deelnemer te hebben verstrekt.

Ik bevestig dat geen enkele druk op de deelnemer is uitgeoefend om hem/haar te doen toestemmen met deelname aan de studie en ik ben bereid om op alle eventuele bijkomende vragen te antwoorden.

Ik bevestig dat ik werk in overeenstemming met de ethische beginselen zoals vermeld in de "Verklaring van Helsinki", de "Goede klinische praktijk" en de Belgische wet van 7 mei 2004 inzake experimenten op de menselijke persoon.

Naan, Voornaam, Datum en handtekening van de vertegenwoordiger van de arts-onderzoeker

Naan, Voornaam, Datum en handtekening van de arts-onderzoeker

Titel van de studie: Invloed van trainingsmodaliteiten op kwaliteit van leven in hartpatienten tijdens revalidatie

III Aanvullende informatie

1: Aanvullende informatie over de organisatie van de studie

Deze bijlage bestaat uit een korte beschrijving van de verschillende raadplegingen voor opvolging die deel uitmaken van de "standard of care" en, indien van toepassing, van de verschillende onderzoeken die normaliter voorzien zijn tijdens deze raadplegingen.

2: Aanvullende informatie over de risico's die verbonden zijn aan de deelname aan deze studie: niet van toepassing

Deze rubriek is in principe niet van toepassing in een observationele studie: de behandeling en de voorgestelde onderzoeken bij de klinische opvolging zijn voorgeschreven in overeenstemming met de voorwaarden voor goede medische praktijken. Ze worden dus aan de patiënten voorgesteld in overeenstemming met de informatieverplichting in het kader van de interactie arts/patiënt en onafhankelijk van een deelname aan de studie.

Als de opdrachtgever echter toch beslist om ze op te nemen, moet hij het feit **benadrukken** dat wat in deze rubriek is vermeld, de risico's zijn die in het kader van standaardverzorging kunnen optreden (en in het bijzonder, niet door de verzekering van de studie worden gedekt!).

3: Aanvullende informatie over de bescherming en de rechten van de deelnemer aan een klinische studie

6.1.2 Ethisch comité

Deze studie werd geëvalueerd door een onafhankelijk ethisch comité [Naam van de EC] dat een gunstig advies heeft uitgebracht [*na raadpleging van het ethisch comité van elk centrum waar deze studie zal uitgevoerd worden*]. De ethische comités hebben als taak de personen die aan klinische studies deelnemen te beschermen. Ze controleren of uw rechten als patiënt en als deelnemer aan een studie gerespecteerd worden, of de studie wetenschappelijk relevant en ethisch verantwoord is.

Hierover brengen de ethische comités een advies uit in overeenstemming met de Belgische wet van 7 mei 2004.

U dient het positief advies van de Ethische Comités in geen geval te beschouwen als een aansporing om deel te nemen aan deze studie.

6.1.3 Vrijwillige deelname

Aarzel niet om alle vragen te stellen die u nuttig vindt voordat u tekent. Neem de tijd om er met een vertrouwenspersoon over te praten, als u dit wenst.

U heeft het recht om niet deel te nemen aan deze studie of met deze studie te stoppen zonder dat u hiervoor een reden hoeft te geven, zelfs al hebt u eerder toegestemd om aan deze studie deel te nemen. Uw beslissing zal in geen geval uw relatie met de arts-onderzoeker en de voortzetting van uw therapeutische behandeling veranderen.

Als u aanvaardt om aan deze studie deel te nemen, ondertekent u het toestemmingsformulier. De arts-onderzoeker zal dit formulier ook ondertekenen en zal zo bevestigen dat hij u de noodzakelijke informatie voor deze studie heeft gegeven. U zult het voor u bestemde exemplaar ontvangen.

Kosten in verband met uw deelname

De opdrachtgever heeft voorzien om het ziekenhuis te vergoeden voor de tijd die de arts-onderzoeker en zijn team aan deze studie besteden. U zult geen vergoeding krijgen voor uw deelname aan deze studie. Uw deelname zal echter voor u geen bijkomende kosten met zich meebrengen.

Vertrouwelijkheidgarantie

Uw deelname aan de studie betekent dat u ermee akkoord gaat dat de arts-onderzoeker gegevens over u verzamelt en dat de opdrachtgever van de studie die gebruikt voor onderzoek en in het kader van wetenschappelijke en medische publicaties.

U hebt het recht om aan de arts-onderzoeker te vragen welke gegevens hij/zij over u heeft verzameld en waarvoor ze gebruikt worden in het kader van de studie. Deze gegevens hebben betrekking op uw huidige klinische situatie maar ook op uw medische voorgeschiedenis en op de resultaten van onderzoeken die werden uitgevoerd voor de behandeling van uw gezondheid volgens de geldende zorgstandaard. U hebt het recht om deze gegevens in te kijken en om verbeteringen te laten aanbrengen indien ze foutief zouden zijn[1].

De arts-onderzoeker is verplicht om deze verzamelde gegevens vertrouwelijk te behandelen.

Dit betekent dat hij zich ertoe verbindt om uw naam nooit bekend te maken in het kader van een publicatie of een conferentie en dat hij uw gegevens zal coderen (uw identiteit zal worden vervangen door een identificatiecode in de studie) voordat hij ze doorgeeft aan de beheerder van de databank

1 Deze rechten zijn bepaald door de wet van 8 december 1992 tot bescherming van de persoonlijke levenssfeer ten opzichte van de verwerking van persoonsgegevens en door de wet van 22 augustus 2002 betreffende de rechten van de patiënt.

(**te identificeren**: naam van de afdeling die de functie van data manager verzekert, naam van de opdrachtgever, lokalisatie).

De arts-onderzoeker en zijn team zullen gedurende de volledige klinische studie de enige personen zijn die een verband kunnen leggen tussen de overgedragen gegevens en uw medisch dossier [2].

De overgedragen persoonlijke gegevens omvatten geen combinatie van elementen waarmee het mogelijk is u te identificeren [3].

De door de opdrachtgever aangestelde beheerder van de onderzoeksgegevens kan u niet identificeren op basis van de overgedragen gegevens. Deze persoon is verantwoordelijk voor het verzamelen van de gegevens die door alle artsen-onderzoekers die deelnemen aan de studie zijn verzameld en voor de verwerking en de bescherming van die gegevens in overeenstemming met de Belgische wet betreffende de bescherming van de persoonlijke levenssfeer.

Om de kwaliteit van de studie te controleren, kan uw medisch dossier worden ingekeken door personen die gebonden zijn aan het beroepsgeheim zoals vertegenwoordigers van de ethische comités, van de opdrachtgever van de studie of een extern auditbureau. Dit kan enkel gebeuren onder strikte voorwaarden, onder de verantwoordelijkheid van de arts-onderzoeker en onder zijn/haar toezicht (of van één van zijn/haar onderzoeksmedewerkers).

De (gecodeerde) onderzoeksgegevens kunnen doorgegeven worden aan Belgische of andere regelgevende instanties, aan de ethische comités, aan andere artsen en/of instellingen die samenwerken met de opdrachtgever.

Ze kunnen ook doorgegeven worden aan andere sites van de opdrachtgever in België en in andere landen waar de normen inzake de bescherming van persoonsgegevens verschillend of minder strikt kunnen zijn. Dit gebeurt dan steeds in gecodeerde vorm zoals hierboven uitgelegd [4].

Uw toestemming om aan deze studie deel te nemen betekent dus ook dat u akkoord gaat dat uw gecodeerde medische gegevens gebruikt worden voor doeleinden die in dit informatieformulier staan beschreven en dat ze worden overgedragen aan bovenvermelde personen en/of instellingen.

De opdrachtgever verbindt zich ertoe om de verzamelde gegevens enkel in het kader van deze studie te gebruiken.

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[2] De wet verplicht om voor klinische studies dit verband met uw dossier gedurende 20 jaar te bewaren.

3 De database met de resultaten van de studie zal dus geen elementen bevatten zoals uw initialen, uw geslacht en uw volledige geboortedatum (dd/mm/jjjj).

4 De opdrachtgever verbindt zich ertoe om het bindend karakter van de Europese richtlijn en van de Belgische wetgeving inzake bescherming van de persoonlijke levenssfeer te respecteren.

[**Of**, indien nodig] De opdrachtgever zal de verzamelde gegevens gebruiken in het kader van de studie waaraan u deelneemt, maar wil ze ook kunnen aanwenden in het kader van andere studies over dezelfde ziekte als de uwe. Buiten de context die wordt beschreven in dit document, kunnen uw gegevens enkel gebruikt worden als een ethisch comité haar goedkeuring heeft gegeven.

6.1.4 Indien u uw toestemming tot deelname aan de studie intrekt, zullen de gecodeerde gegevens die al verzameld waren vóór uw terugtrekking, bewaard worden. Hierdoor wordt de geldigheid van de studie gegarandeerd. Er zal geen enkel nieuw gegeven aan de opdrachtgever worden doorgegeven.

6.1.5 Verzekering

In een observationele studie is het enige mogelijke risico een probleem met de maatregelen die werden genomen om de vertrouwelijkheid van uw persoonsgegevens te beschermen. De opdrachtgever is, ook indien er geen sprake is van fout, aansprakelijk voor de schade die u als deelnemer - of in geval van overlijden uw rechthebbenden - oplopen en die rechtstreeks of onrechtstreeks te wijten is aan de deelname aan deze studie. Hiervoor heeft de opdrachtgever een verzekeringscontract afgesloten (naam verzekering, polisnummer, contactgegevens)[5].

[5] Conform artikel 29 van de Belgische wetgeving inzake experimenten op de menselijke persoon (7 mei 2004)

Auteursrechtelijke overeenkomst

Ik/wij verlenen het wereldwijde auteursrecht voor de ingediende eindverhandeling:
Improvements in cardiovascular risk and physical fitness during cardiac rehabilitation: which improvements are related to reductions in risk for major adverse cardiac events during follow-up?

Richting: **master in de revalidatiewetenschappen en de kinesitherapie-revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen**
Jaar: **2017**

in alle mogelijke mediaformaten, - bestaande en in de toekomst te ontwikkelen - , aan de Universiteit Hasselt.

Niet tegenstaand deze toekenning van het auteursrecht aan de Universiteit Hasselt behoud ik als auteur het recht om de eindverhandeling, - in zijn geheel of gedeeltelijk -, vrij te reproduceren, (her)publiceren of distribueren zonder de toelating te moeten verkrijgen van de Universiteit Hasselt.

Ik bevestig dat de eindverhandeling mijn origineel werk is, en dat ik het recht heb om de rechten te verlenen die in deze overeenkomst worden beschreven. Ik verklaar tevens dat de eindverhandeling, naar mijn weten, het auteursrecht van anderen niet overtreedt.

Ik verklaar tevens dat ik voor het materiaal in de eindverhandeling dat beschermd wordt door het auteursrecht, de nodige toelatingen heb verkregen zodat ik deze ook aan de Universiteit Hasselt kan overdragen en dat dit duidelijk in de tekst en inhoud van de eindverhandeling werd genotificeerd.

Universiteit Hasselt zal mij als auteur(s) van de eindverhandeling identificeren en zal geen wijzigingen aanbrengen aan de eindverhandeling, uitgezonderd deze toegelaten door deze overeenkomst.

Voor akkoord,

Stassen, Lotte **Snoekx, Dennis**