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Faculteit Geneeskunde en Levenswetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

Is there a relationship between improvement of physical fitness and mortality or hospitalization in patients with heart failure and coronary artery disease?

Martijn Grauwels
Wenche Janssens

Eerste deel van het scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie

PROMOTOR :

Prof. dr. Dominique HANSEN

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Master thesis part 1

Is there a relationship between improvement of physical fitness and mortality or hospitalization in patients with heart failure and coronary artery disease?

Highlights:

- Peak VO_2 increases in patients with heart failure as a result of physical rehabilitation.
- Starting physical rehabilitation in the acute phase after myocardial infarction (LVEF 30-50%) in younger patients leads to greater increment in peak VO_2.

Students: Grauwels Martijn and Janssens Wenche

Promotor: Prof. Dr. Hansen Dominique

CONTEXT OF MASTER THESIS

This master thesis can be situated in the research domain of cardiorespiratory rehabilitation.

Physical fitness is an important prognostic factor in cardiovascular diseases and it is also related to mortality. Nowadays, healthy aging is an important topic in the rehabilitation. Therefore, it is important to know if there is a relationship between improvement of physical fitness and mortality or hospitalization in patients with heart failure and coronary artery disease. This is also the research question of this master thesis.

In the first part of this duo-master thesis the central format was applied. Together with Prof. Dr. Dominique Hansen both the research question and the literature search were determined. It is a single study and a new research project.

In master thesis part two, data of patients with cardiovascular diseases who already followed a rehabilitation program in Rehabilitation and Health Centre Hasselt (ReGo) will be analyzed.

Both students conducted the literature search. One screened articles for subquestion one and three dealing with the inclusion criteria and the other student screened the articles for subquestion two. These articles were analyzed separately and hereafter controlled and discussed together. The master thesis and the study protocol were written together.

A new research protocol was created and the students will define the parameters and determine both ventilatory thresholds and peak VO_2. Hospitalization and mortality rates will have to be analyzed together with the corresponding ventilatory thresholds and peak VO_2 to investigate if there is a relationship between changes in peak VO_2 or anaerobic threshold and hospitalization or mortality in patients with heart failure and coronary artery disease.

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PART 1: LITERATURE SEARCH

PART 2: RESEARCH PROTOCOL

PART 1: LITERATURE SEARCH

1. Abstract

Background: Cardiovascular diseases (CVD) are the most common cause of death worldwide. In the prognosis of CVD, physical fitness is important and related to mortality. Peak VO_2 and anaerobic threshold (AT) are indicators of aerobic capacity and are important in the prognosis of heart diseases. This literature study examines the relationship between the improvement of peak VO_2 or AT and mortality or hospitalization in patients with heart failure (HF) and coronary artery disease (CAD).

Methods:
PubMed was used as database. Four search strategies were used including meta-analyses and systematic reviews. An extra search strategy was used for search strategy two and three which included RCT's.

Results:
15 articles (eight RCT's, seven meta-analyses) were included and analyzed concluding that physical training increases peak VO_2 in HF. The sooner physical therapy is started after myocardial infarction, the more peak VO_2 increases. Study results were difficult to compare, due to the varied intervention characteristics. The relationship between changes in peak VO_2 or AT and mortality or hospitalization in patients with HF and CAD is unknown.

Discussion and conclusion:
Further research is needed to investigate the relationship between changes in peak VO_2 or AT and mortality or hospitalization in HF and CAD patients.

Aim of the literature search: To investigate the relationship between improvement of physical fitness and mortality or hospitalization in patients with HF and CAD.

Operationalization of research question: A new research project under supervision of Prof. Dr. Dominique Hansen.

Most important key words:
Cardiovascular disease, peak VO_2, anaerobic threshold, mortality, hospitalization.

2. Introduction

According to the World Health Organization (WHO) (www.who.int), cardiovascular diseases (CVD) (most important CAD and HF) are the most common cause of death all over the world. Moreover, CVD accords for 31% of yearly deaths globally. It involves diseases of the heart, the blood vessels or vascular diseases of the brain where atherosclerosis affects the circulation by formation of plaques on the wall of the blood vessels (O'Sullivan B. S., Schmitz T. J. and Fulk G. D. (2014); Mendis S., Puska P. & Norrving B. 2011).

According to the WHO (www.who.int), unhealthy diet, excessive use of alcohol and smoking are important risk factors of heart diseases through its effect on blood pressure, lipid profile, glycemic control and body composition. Besides those risk factors, physical fitness is one of the most important prognostic factors of heart diseases such as CVD and it is also related to mortality (Biswas et al., 2015; Warburton, Nicol, & Bredin, 2006).

The maximal oxygen consumption (VO_2max) indicates the cardiorespiratory fitness of an individual (Ross et al., 2016). Together with the anaerobic threshold (AT) it is the best indicator for the aerobic capacity of an individual (O'Sullivan et al., 2014). In healthy people a lifestyle with physical activity results in a higher aerobic capacity and life expectancy compared to a sedentary lifestyle (Pina et al., 2003; Reimers, Knapp, & Reimers, 2012; Wen et al., 2011).

Because peak VO_2 and AT are really important in the prognosis of heart diseases, this literature search wants to investigate: (1) what the impact of physical rehabilitation on this parameter is in patients with heart failure (HF) and coronary artery disease (CAD), (2) what the impact of physical rehabilitation is on mortality and hospitalization in patients with HF and CAD and (3) what the relationship is between changes in peak VO_2 or AT and prognosis in patients with HF and CAD.

This literature search is very important for physiotherapists to better understand the importance of physical rehabilitation in patients with HF and CAD.

3. Method

3.1 Research question

The main goal of this literature search was to investigate a possible relationship between improvement of physical fitness and the mortality or hospitalization in patients with heart failure and coronary artery disease.

The following PICO is the summary of the research question:

P: Patients with cardiovascular disease
I: Physical training
C: No physical training
O: Peak VO_2, anaerobic threshold, mortality, hospitalization

The research question is divided in three subquestions:

1. What is the impact of physical rehabilitation on peak VO_2 and AT in patients with HF and CAD?
2. What is the impact of physical rehabilitation on mortality and hospitalization in patients with HF and CAD?
3. What is the relationship between changes in peak VO_2 or anaerobic threshold and mortality or hospitalization in patients with HF and CAD?

3.2 Literature search

PubMed has been used to search the literature. The following search terms were used: 'cardiovascular disease', 'physical training', 'exercise', 'rehabilitation', 'resistance training', 'peak VO_2', 'anaerobic threshold', 'mortality' and 'hospitalization'. There were no MeSH-terms available for 'physical training' and 'peak VO_2'. For these terms Title/Abstract was used.

Four search strategies were used to find articles specifically for each part of the research question.

The first search strategy was developed to obtain articles that investigate the impact of physical rehabilitation on peak VO_2 and AT in patients with HF and CAD (subquestion 1). The following terms were combined with 'AND', 'OR' or 'NOT': 'cardiovascular disease', 'physical training', 'exercise', 'rehabilitation', 'resistance training', 'peak VO_2' and 'anaerobic threshold' (see table 1).

The second search strategy was developed to obtain articles investigating the impact of physical rehabilitation on mortality and hospitalization in patients with HF and CAD (subquestion 2). The following

terms were combined with ‘AND’, ‘OR’ or ‘NOT’: ‘cardiovascular disease’, ‘physical training’, ‘exercise’, ‘rehabilitation’, ‘resistance training’, ‘mortality’ and ‘hospitalization’ (see table 2).

The third search strategy was developed to obtain articles that investigate the relationship between changes in peak VO_2 or anaerobic threshold and mortality or hospitalization in patients with HF and CAD (subquestion 3). The following terms were combined with ‘AND’ or ‘OR’: cardiovascular disease’, ‘peak VO_2’, ‘anaerobic threshold’, ‘mortality’ and ‘hospitalization’ (see table 3).

As a fourth and final step all terms where combined with ‘AND’, ‘OR’, or ‘NOT’ (see table 4). This search strategy was developed to obtain articles that investigate a combination of the previous search strategies.

In search strategies one and two, only meta-analyses were selected. In the third search strategy and in the final step both meta-analyses and systematic reviews were selected.
The selection of meta-analyses and systematic reviews was possible only in PubMed and not in other databases e.g. Web of Science, Pedro and Cinahl. Therefore, it was not possible to use these databases.

Google-Scholar didn’t provide any additional articles when searching for more recent articles on top of those found in PubMed. No more recent systematic reviews or meta-analyses are found using this source.

Also, the year of publication, the language or human have not been used as selection criteria in PubMed.

When no articles could be found using the said search strategies, an extra search strategy was used.
The extra search strategy contained two parts. In the first part, articles from the reference list of the unique articles for the search strategy were screened for the inclusion and exclusion criteria. Only randomized controlled trials were included. In the second part the PubMed database was searched again. The entire search strategy was repeated, now searching for randomized controlled trials instead of meta-analyses or systematic reviews. The articles also needed to be published after publication date of the unique articles of part one.

3.3. Selection criteria

For each search strategy, specific criteria were used to check the applicability of the found articles for the corresponding subquestion. These criteria are listed in table 5.

In addition to the criteria for each search strategy, articles were excluded for the following reasons: (1) patients younger than 18 years, (2) unsupervised intervention, (3) the control group received exercise intervention and (4) patients received resistance training only.

3.4 Quality assessment

To assess the quality of meta-analyses and systematic reviews, the PRISMA-checklist for meta-analyses and systematic reviews was used (see table 7.1 and 7.2) (Moher, Liberati, Tezlaff & Altman, 2009). This checklist was converted to a checklist with three possible answers (yes, no, not applicable). For each item a score of zero or one was given when the item had respectively a negative or a positive influence on the quality of the article. When an item was irrelevant for a specific article, 'not applicable' was mentioned and no score was given. This was done to make a comparison between the quality of the included articles. In terms of content, no adjustments were made.

The CONSORT 2010 Checklist was used to assess the quality of the randomized controlled trials (*CONSORT 2010 Checklist*, 2010). If the item in the checklist was reported in the article, the page number was mentioned in the checklist and scored one. If not mentioned but relevant, a score zero was given. If an item was irrelevant, 'not applicable' was mentioned and no score was given.

3.5 Data extraction

Peak VO_2, anaerobic threshold, hospitalization rates and mortality rates were the extracted data from the included studies.

Within each subquestion the corresponding results were compared.

4. Results

4.1 Results study selection

First, the articles on PubMed were screened for each search strategy. If they did not meet the inclusion criteria of the respective search strategy the articles were excluded. Thereafter, all the articles were put together and duplicates were removed. The unique articles were screened again and in addition to the selection criteria for each search strategy, articles were excluded based on the exclusion criteria. The process of the study selection is shown in figure 1.

After the study selection, no articles remained in search strategy two and three.

The extra search strategy as mentioned in the method of study selection was done for search strategy two (2.2 and 2.3) and three (3.2 and 3.3). The articles were selected the same way as in search strategy one. Eight articles remained for strategy 2.2 and 2.3 and two articles for strategy 3.2 and 3.3. The process of extra study selection is shown in figure 2 and 3.

Table 6 gives an overview of the excluded studies and the reason of exclusion.

In total, search strategy one had a sample size of 7251 patients. Search strategy two (2.2 and 2.3) and three (3.3 and 2.3) had a sample size of respectively 3909 and 142 patients. The total sample size in this literature search is 11248 patients. Based on these sample sizes, the results are discussed per search strategy.

4.2 Results quality assessment

None of the included meta-analyses that were assessed by the PRISMA-checklist for meta-analyses and systematic reviews (Moher et al., 2009) mentioned the strength of evidence for each outcome. Four meta-analyses lost between three and six points. Gomes Neto, Menezes, and Oliveira Carvalho (2014) lost 7 points.

From all the randomized controlled trials, assessed by the CONSORT 2010 Checklist (*CONSORT 2010 Checklist*, 2010), Briffa et al. (2005) only lost three points and Denollet and Brutsaert (2001) lost seven points. The other randomized controlled trials lost five or six points in their quality assessment. Three assessed randomized controlled trials were not randomized.

The complete quality assessment of the included articles can be found in table 7.1 and 7.2.

4.3 Results data extraction

An overview of the relevant intervention characteristics of the included studies for each corresponding subquestion can be found in table 8. Table 9 gives an overview of the population, outcome measures and the results.

4.3.1 Impact of physical rehabilitation on peak VO_2 and AT in patients with HF and CAD

4.3.1.1 Heart failure

High intensity exercise training was defined as training at 90-95% peak VO_2, 80-90% peak HR or 80% HRR. When compared to the control group a significant mean difference (MD) of 3,3 ml/kg/min (23%) for peak VO_2 was found in the high intensity exercise group after the training program with a session duration of 30-60 minutes and a program duration of 8-16 weeks. In the subanalysis a significant increase of peak VO_2 (MD = 3,94 ml/kg/min) was found for the continuous but not for the interval training. No significant increase was found at low intensity training. These results were applicable on each NYHA classification (I, II, III and IV), but only HF patients with a reduced left ventricular ejection fraction (LVEF) (< 40%) (Ismail, McFarlane, Dieberg, & Smart, 2014; Ismail, McFarlane, Nojoumian, Dieberg, & Smart, 2013).

When HF patients followed a dance therapy intervention at an intensity of 70% peak VO_2 or 13-14 Borg, a significant increase of peak VO_2 was found in the intervention group with a mean difference of 4,86 ml/kg/min comparing to the control group. These results were only applicable on HF patients with a NYHA classification of II or III (Gomes Neto et al., 2014).

In (Smart et al., 2012), HF patients with a LVEF < 50% participated in a cycling intervention. Compared to the control group, the group that underwent cycling intervention had a significant higher increase (17,8%) of peak VO_2 compared to the control group (1,4%). Peak VO_2 increased more than 5% in 80% of all the patients in the intervention group. Only 7% showed a negative response (Smart et al., 2012).

4.3.1.2 Coronary artery disease

4.3.1.2.1 Myocardial infarction

Zhang et al. (2016) made a distinction in the initiation time of the exercise intervention in younger patients (mean age: 58) after a myocardial infarction (MI) with a LVEF of 30-50%: (1) acute phase: 7 hours - 3 days, (2) healing phase: 7 - 28 days, (3) healed phase: more than 29 days.
When performing exercise training at an intensity of 50-85% peak VO_2, 70-90% peak HR or 60-85% HRR, the peak VO_2 showed a significant increase in the acute phase compared to the control group with a mean difference of 1,52 ml/kg/min. Repeating the same exercise training in the healing or healed phase, the peak VO_2 showed a significant increase in peak VO_2 compared to the control group with a mean difference of respectively 1,14 ml/kg/min and 0,62 ml/kg/min.

4.3.2 Impact of physical rehabilitation on mortality and hospitalization in patients with HF and CAD

4.3.2.1 Heart failure

In Zwisler et al. (2008) HF patients performed aerobic exercise during an intervention of six weeks. After 12 months of follow-up no significant difference was found in mortality and hospitalization.

4.3.2.2 Coronary artery disease

4.3.2.2.1 All CAD's

A significant lower mortality rate was found in patients suffering from CAD (Dendale et al., 2005; Denollet & Brutsaert, 2001). In Dendale et al. (2005) the CAD patients performed aerobic exercise at an intensity that was close to the anaerobic threshold level. They performed the exercise three times a week for 60 minutes during an intervention that lasted three months. After 15 months of follow-up there was a significantly lower mortality rate in the rehabilitation group compared to the control group (1% vs 6%). In Denollet and Brutsaert (2001) patients were divided into two groups: low-risk patients and high-risk patients. Low-risk patients trained at an intensity of 65-85% of their peak VO_2. High-risk patients trained at an intensity that was 50-75% of their peak VO_2. All patients performed the aerobic exercise two or three times a week during an intervention of three months or more. After nine years of follow-up there was a significant lower mortality rate in the rehabilitation group compared to the control group (4% vs 17%).

In another intervention with aerobic exercise training, no significant difference was found between the patients undergoing intervention and the control group. in terms of mortality and hospitalization (Dendale, Hansen, Berger, & Lamotte, 2008; Zwisler et al., 2008).

4.3.2.2.2 Myocardial infarction

When patients suffering from acute MI performed aerobic exercise in an intervention during four to eight weeks, no significant difference in mortality was found between the intervention group and the control group (La Rovere, Bersano, Gnemmi, Specchia, & Schwartz, 2002; Oldridge et al., 1991; West, Jones, & Henderson, 2012).
In Briffa et al. (2005) aerobic exercise was combined with resistance training. For six weeks patients suffering from acute MI performed exercise three times a week for 60 to 90 minutes. After 12 months of follow-up a higher rehospitalization rate was found in the conventional care group compared to the intervention group, but this was not significant.
West et al. (2012) performed an intervention of six to eight weeks of comprehensive cardiac rehabilitation. After 12 months of follow-up no difference was found in rehospitalization between the rehabilitation group and the control group.

4.3.3 Relationship between changes in peak VO_2 or anaerobic threshold and mortality or hospitalization in patients with HF and CAD

4.3.3.1 Heart failure

According to Belardinelli, Georgiou, Cianci, and Purcaro (1999) peak VO_2 is one of the strongest predictors for re-hospitalization in patients with HF. Peak VO_2 significantly increased after two months of cycling exercise training, at a frequency of 3 times a week. No significant increase was seen in the control group. After 14 months (12 months training at a frequency of 2 times a week) the value of peak VO_2 barely changed. Patients in the control group were significantly more hospitalized (RR = 0,29) and had significantly more cardiac deaths (RR = 0,37) compared to trained patients. Patients who had a cardiac event and died after the physical training, had a significant lower peak VO_2 after physical training than patients who did not die.

When combining aerobic (cycling) exercise at an intensity of 50% of peak VO_2 and resistance training at an intensity of 20-25% of 1RM no significant increase of peak VO_2 was found in the exercise group or the control group. Also, no significant difference was found between both groups. After 12 months two patients in the exercise group and five in the control group were hospitalized. After 28 months the total of hospitalized

patients increased to seven in the exercise group and 12 in the control group. Two patients in the exercise and two patients in the control group died (Jonsdottir, Andersen, Sigurosson, & Sigurosson, 2006).

4.3.3.2 Coronary artery disease

No relevant studies were found for CAD concerning subquestion three.

5. Discussion

5.1 Reflection on the quality assessment

The meta-analyses of search strategy one received a score on the PRISMA-checklist for meta-analyses and systematic reviews (Moher, Liberati, Tezlaff & Altman, 2009). It was not possible to interpret the quality assessment based on this score. Because the checklist was transformed into a yes/no/not applicable checklist, there was no normative data available to conclude if the article had a high or low quality. It was only possible to compare the checklists of the articles. With a score of 16 on a total of 23, Gomes Neto et al. (2014) was an outlier that lost more than 6 points on the quality of the article. This article did not mention a clear research question, a study selection process and a total number of screened studies, which are essential items for a meta-analysis. Therefore, it had a lower quality compared to the others.

Comparison of the scores on the CONSORT 2010 Checklist (*CONSORT 2010 Checklist*, 2010) performed on the randomized controlled trials was not possible due to the difference in the possible maximum scores for each study. However, it was possible to compare the number of lost points. With only three points lost, Briffa et al. (2005) had the highest quality of the included randomized controlled trials. Most points were lost by Denollet and Brutsaert (2001) with a loss of seven points. However, this was fairly comparable with the other randomized controlled trials who all lost five or six points.

5.2 Reflection on findings related to the research question

5.2.1 Impact of physical rehabilitation on peak VO_2 and AT in patients with HF and CAD

For patients with HF and reduced ejection fraction (< 40%) high intensity exercise training improves peak VO_2 (Ismail et al., 2014; Ismail et al., 2013). For vigorous and moderate training, it was not possible to make a statement about peak VO_2 because the intervention was home-based, and this could skew the results.

Dance therapy at a lower intensity (Gomes Neto et al., 2014) than high intensity exercise training (Ismail et al., 2014; Ismail et al., 2013) also increased peak VO_2 in patients with HF. This increase was even higher than with high intensity exercise training. Thus, exercise at lower intensity had a more positive effect on peak VO_2. (Gomes Neto et al., 2014). The higher increase at lower intensity could be hypothesized by the longer program duration or the inclusion of only HF patients with NYHA II or III and no reduced LVEF.

Smart et al. (2012) investigated exercise training in patients with HF at a wide range of intensity (50-95% peak VO_2) and due to the low intensity in several studies, this could hypothesize the less high increase of peak VO_2 in patient with HF and reduced LVEF. This could be in line with the results of a recent study which

concluded that the increase in high intensity training is significantly higher compared to moderate intensity training (Hannan et al., 2018). The study of Hannan et al. (2018) only included patients with normal LVEF, so the hypothesis could not be confirmed.

The initiation time of exercise training plays an important role in the improvement of peak VO_2 after a post-myocardial infarction (LVEF 30-50%) in younger patients. Starting exercise training in the acute phase resulted in the highest improvement of peak VO_2 (Zhang et al., 2016). No information was available about the initiation time in elderly patients.

In all the articles the intervention had a session duration between 30 and 60 minutes, but the intensity, frequency, program duration and population are not equal. This is why no general conclusion could be made based on these characteristics.

5.2.2 Impact of physical rehabilitation on mortality and hospitalization in patients with HF and CAD

Only Dendale et al. (2005) and Denollet and Brutsaert (2001) showed a significant decrease in mortality rate in patients with CAD compared with a control group. In both studies patients performed aerobic exercise combined with psychological therapy three times a week for three months. The significant decrease in mortality rate could be due to this intervention mode and the intervention characteristics.

In the intervention of Dendale et al. (2005) and Dendale et al. (2008) the same intervention mode, intensity, frequency and session duration were used. Dendale et al. (2005) showed a significant improvement in mortality after 15 months of follow-up (short-term), but Dendale et al. (2008) did not show a significant difference in mortality after four and a half years of follow-up (long term). A difference in program duration might also have had an influence on the results.

Comparison of the different studies of subquestion two was difficult because of the large variety of the intervention characteristics. The used training intensities differed and in Briffa et al. (2005), West et al. (2012) and Zwisler et al. (2008) the training intensity was not even mentioned. The duration of each session was not mentioned in Denollet and Brutsaert (2001), West et al. (2012) and Zwisler et al. (2008). The large differences in follow-up also might have had an influence on the results.

After physical rehabilitation no significant difference was found for mortality in patients suffering from an acute MI (Oldridge et al., 1991). The specific inclusion of patients with depression, anxiety or both might have had an influence on the outcome.

5.2.3 Relationship between changes in peak VO_2 or anaerobic threshold and mortality or hospitalization in patients with HF and CAD

According to Belardinelli et al. (1999) a short aerobic training period of two months improved the peak VO_2 just as much as a longer training period of 14 months for patients with chronic HF. This could be due to the higher training frequency in the first two months of training. Patients who died after the intervention did not show an improvement in peak VO_2 after exercise training. Therefore, peak VO_2 could be a predictor of mortality in HF patients. Patients in the control group showed no significant increase in peak VO_2 and significantly more hospitalizations and cardiac deaths were reported. It could be hypothesized that an increase of peak VO_2 in HF patients results in less hospitalizations and cardiac deaths.

A combination of cycling and resistance training did not improve peak VO_2 and did not lower the hospitalization rate in HF patients (Jonsdottir et al., 2006). This could be due to the low intensity of the cycling training and resistance training. There was even a rise in hospitalization rate in the intervention group, but it was not known if the results for mortality and hospitalization rates were significant (Jonsdottir et al., 2006). When comparing these results with the results of the recent study of Jewiss, Ostman, and Smart (2016), peak VO_2 increases significantly when performing aerobic training and resistance training at a higher intensity. But also, no significant decrease of hospitalization was found. Thus, a possible relationship between peak VO_2 and hospitalization rate is unclear.

5.2.4 General reflection

5.2.4.1 Heart failure

Physical exercise in a rehabilitation program increases peak VO_2 in HF patients (Gomes Neto et al., 2014; Ismail et al., 2014; Ismail et al., 2013; Smart et al., 2012; Zhang et al., 2016).
There is no significant difference in hospitalization and mortality after a physical exercise program according to Zwisler et al. (2008) and Jonsdottir et al. (2006), but Belardinelli et al. (1999) shows an association between increase of peak VO_2 and decrease of hospitalization and mortality in patients with HF.

5.2.4.2 Coronary artery disease

According to Dendale et al. (2005) and Denollet and Brutsaert (2001) physical exercise significantly decreases mortality in patients with CAD. This result contradicts the findings of Dendale et al. (2008) who reported no significant decrease in mortality after the physical exercise program.

5.2.4.3 Myocardial infarction

Starting a physical exercise program in the acute phase in younger patients after a MI (LVEF 30-50%) results in the highest significant increase of peak VO_2 according to Zhang et al. (2016). Mortality and hospitalization were not significantly different after an aerobic or a combined exercise program of aerobic exercise and resistance training (Briffa et al., 2005; La Rovere et al., 2002; Oldridge et al., 1991; West et al., 2012).

5.3 Reflection on strengths and weaknesses of literature search

Table 10 gives an overview of the strengths and weaknesses of the included studies.

Some of the major strengths are:

- Inclusion and exclusion criteria were well described in all the articles.
- The intervention in the included articles was supervised.

Some of the major weaknesses are:

- Several studies did not mention a follow-up period.
- Most of the studies investigated mainly men.
- Seven articles were published more than ten years ago (no recent articles).

There are also some strengths and weaknesses in this literature search. One of the most important weaknesses is that the level of evidence for subquestion two and three was lower than for subquestion one because the articles included in subquestion two and three are randomized controlled trials while the articles in subquestion one are meta-analyses. Another weakness is the use of only one database. A major strength of this literature search is that the articles were not filtered on publication date, language and free full text.

5.4 Recommendations for Future Research

There are several recommendations to improve future research investigating the relationship between improvement of physical fitness and the mortality and hospitalization of patients with a HF and CAD. Firstly, more research is needed to investigate which intervention mode and training parameters (session duration, program duration and training intensity) are optimal to improve physical fitness and reduce mortality and hospitalization in patients with HF and CAD.

It is not clear whether there is a difference in gender because mainly men were investigated. In future research, more women need to be included.
Since no information was found about the influence of physical exercise on peak VO_2 and the relationship between peak VO_2 and mortality of hospitalization in patients with CAD in general, further research is needed.
Furthermore, future research is needed to investigate the long-term effects of exercise training because several studies had a short-term follow-up.

Next, no articles were found about the anaerobic threshold. However, the anaerobic threshold is more important for patients than peak VO_2. When performing exercise, tidal volume decreases and minute ventilation progressively increases when intensity increases. When approaching the anaerobic threshold, the person will experience shortness of breath (Albouaini, Egred, Alahmar, & Wright, 2007; Mirmohamadsadeghi, Vesin, Lemay, & Deriaz, 2015).
The anaerobic threshold is higher in trained adults compared to sedentary adults (Grigaliuniene et al., 2013). So, they will experience shortness of breath at a higher intensity than sedentary adults. Therefore, it is useful to work with the anaerobic threshold because the patients can feel when they reach this threshold. Future research is needed to investigate the relationship between improvement of anaerobic threshold and hospitalization and mortality.

Lastly, little is known about the hospitalization rate. Since a higher hospitalization rate could reduce the quality of life of an individual, future research needs to be done about the relationship between improvement of physical fitness and hospitalization rates.

6. Conclusion

Physical rehabilitation increases peak VO_2 in patients with heart failure, but the relationship for patients with coronary artery disease remains inconclusive. Peak VO_2 increases most when starting physical rehabilitation in the acute phase after a myocardial infarction (LVEF 30-50%) in younger patients. It is not possible to make a conclusion for elderly and patients with heart failure and coronary artery disease in general. The relationship between changes in peak VO_2 or anaerobic threshold and mortality or hospitalization in patients with heart failure and coronary artery disease remains inconclusive.

7. List of references

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9. Appendix 1

Table 1: Search strategy 1

	MeSH terms and keywords	Hits December 2017	Hits April 2018
#1	“Cardiovascular Diseases"[Mesh]	2161568	2181812
#2	Physical training [All Fields]	189568	194899
#3	"Exercise"[Mesh]	159631	163828
#4	"Rehabilitation"[Mesh]	267111	271417
#5	"Resistance Training"[Mesh]	6057	6342
#6	#2 OR #3 OR #4 NOT #5	531174	542014
#7	Vo2 peak [All Fields]	3789	3861
#8	"Anaerobic Threshold"[Mesh]	3018	3042
#9	#7 OR #8	6560	6653
#10	#1 AND #6 AND #9	718	725
#11	#10 AND Meta-analysis [ptyp]	17	17

Table 2: Search strategy 2

	MeSH terms and keywords	Hits December 2017	Hits April 2018
#12	#1	2161568	2181812
#13	#6	531174	542014
#14	"Mortality"[Mesh]	337332	340644
#15	"Hospitalization"[Mesh]	202872	205627
#16	#14 OR #15	518132	525865
#17	#12 AND #13 AND #16	3364	3432
#18	#12 AND #13 AND #16 AND Meta-analysis [ptyp]	46	47

Table 3: Search strategy 3

	MeSH terms and keywords	Hits December 2017	Hits April 2018
#19	#1	2161568	2181812
#20	#9	6560	6653
#21	#16	518132	525865
#22	#19 AND #20 AND #21	76	77
#23	#19 AND #20 AND #21 AND Meta-Analysis[ptyp]	2	2
#24	#19 AND #20 AND #21 AND (Meta-Analysis[ptyp] OR systematic[sb])	4	4

Table 4: Search strategy 4

	MeSH terms and keywords	Hits December 2017	
#25	#1 AND #6 AND #9 AND #16 AND (Meta-Analysis[ptyp] OR systematic[sb])	3	3

Table 5: **Selection criteria per search strategy**

Search strategy 1
• Cardiovascular disease
• Intervention: Aerobic exercise
• Outcomes
  ○ VO_2 peak or anaerobic threshold
• Meta-analysis
	Search strategy 2
	• Cardiovascular disease
	• Intervention: Aerobic exercise
	• Outcomes
	  ○ Mortality or hospitalization
	• Meta-analysis

Search strategy 3
• Cardiovascular disease
• Outcomes
  ○ VO_2 peak or anaerobic threshold
  ○ Mortality or hospitalization
• Meta-analysis or systematic review
	Search strategy 4
	• Cardiovascular disease
	• Intervention: Aerobic exercise
	• Outcomes
	  ○ VO_2 peak or anaerobic threshold
	  ○ Mortality or hospitalization
	• Meta-analysis or systematic review

Table 6: Excluded studies

Author	Title	Reason of exclusion
("Comparison of a rehabilitation programme, a counselling programme and usual care after an acute myocardial infarction: results of a long-term randomized trial. P.RE.COR. Group," 1991)	Comparison of a rehabilitation programme, a counselling programme and usual care after an acute myocardial infarction: results of a long-term randomized trial	No full text available
("Influence on lifestyle measures and five-year coronary risk by a comprehensive lifestyle intervention programme in patients with coronary heart disease," 2003)	Influence on lifestyle measures and five-year coronary risk by a comprehensive lifestyle intervention programme in patients with coronary heart disease	No training of physical fitness
(Abraham et al., 2004)	Effects of cardiac resynchronization on disease progression in patients with left ventricular systolic dysfunction, an indication for an implantable cardioverter-defibrillator, and mildly symptomatic chronic heart failure.	Irrelevant intervention
(Ades, Pashkow, & Nestor, 1997)	Cost-effectiveness of cardiac rehabilitation after myocardial infarction	No training of physical fitness
(Ahmad et al., 2016)	Prognostic Implications of Long-Chain Acylcarnitines in Heart Failure and Reversibility With Mechanical Circulatory Support.	No exercise intervention and partly unsupervised
(Alter, Oh, & Chong, 2009)	Relationship between cardiac rehabilitation and survival after acute cardiac hospitalization within a universal health care system	Partly unsupervised
(Anderson et al., 2016)	Exercise-based cardiac rehabilitation for coronary heart disease	Not every included article was supervised
(Anderson et al., 2017)	Patient education in the management of coronary heart disease	No training of physical fitness
(Anker et al., 2015)	A prospective comparison of alginate-hydrogel with standard medical therapy to determine impact on functional capacity and clinical outcomes in patients with advanced heart failure (AUGMENT-HF trial).	Irrelevant intervention
(Arena, Myers, Forman, Lavie, & Guazzi, 2013)	Should high-intensity-aerobic interval training become the clinical standard in heart failure	No systematic review of meta-analysis
(Austin, Williams, Ross, & Hutchison, 2008)	Five-year follow-up findings from a randomized controlled trial of cardiac rehabilitation for heart failure	No RCT
(Austin, Williams, Ross, Moseley, & Hutchison, 2005)	Randomised controlled trial of cardiac rehabilitation in elderly patients with heart failure.	No VO_2 peak, mortality or hospitalization
(Banks et al., 2016)	Response to Exercise Training and Outcomes in Patients With Heart Failure and Diabetes Mellitus: Insights From the HF-ACTION Trial.	Partly unsupervised
(Banks et al., 2016)	Response to exercise training and outcomes in patients with heart failure and diabetes mellitus: insights from the HF-ACTION Trial	Completion date before 2017/11/01

(Beauchamp et al., 2013)	Attendance at cardiac rehabilitation is associated with lower all-cause mortality after 14 years of follow-up	No control group
(Bengtsson, 1983)	Rehabilitation after myocardial infarction: a controlled study	No prognostic outcome
(Bindawas, Vennu, & Moftah, 2017)	Improved functions and reduced length of stay after inpatient rehabilitation programs in older adults with stroke: A systematic review and meta-analysis of randomized controlled trials	No prognostic outcome
(Bondestam, Breikss, & Hartford, 1995)	Effects of early rehabilitation on consumption of medical care during the first year after acute myocardial infarction in patients ≥ 65 years of age	No training of physical fitness
(Boyde et al., 2017)	The self-care educational intervention for patients with heart failure: a study protocol	Completion date before 2017/11/01
(Cabello, Burls, Emparanza, Bayliss, & Quinn, 2016)	Oxygen therapy for acute myocardial infarction.	No training of physical fitness
(Carlsson, 1998)	Serum cholesterol, lifestyle, working capacity and quality of life in patients with coronary artery disease. Experiences from a hospital-based secondary prevention programme	No prognostic outcome
(Chen & Li, 2013)	Self-monitoring and self-management of oral anticoagulation	No training of physical fitness
(Chen & Li, 2013)	Safety and efficacy of exercise training in elderly heart failure patients: a systematic review and meta-analysis	Not every included article was supervised
(Chien, Lee, Wu, Chen, & Wu, 2008)	Home-based exercise increases exercise capacity but not quality of life in people with chronic heart failure: a systematic review.	No supervision
(Chung et al., 2010)	Ratio of early mitral inflow peak velocity to flow propagation velocity predicts training effects of cardiac rehabilitation in patients after acute myocardial infarction	Irrelevant intervention
(Cipriano et al., 2014)	Aerobic exercise effect on prognostic markers for systolic heart failure patients: a systematic review and meta-analysis.	Outcome: no peak VO_2
(Clark, Hartling, Vandermeer, & McAlister, 2005)	Meta-analysis: secondary prevention programs for patients with coronary artery disease.	Not every included article was supervised
(Cordeiro et al., 2016)	Inspiratory muscle training and functional capacity in patients undergoing cardiac surgery	Completion date before 2017/11/01
(Cornelis et al., 2015)	Prognostic respiratory parameters in heart failure patients with and without exercise oscillatory ventilation - a systematic review and descriptive meta-analysis.	Irrelevant intervention
(Cramer et al., 2015)	Mind-body medicine in the secondary prevention of coronary heart disease	Not every included article had a control group without physical component
(Davidson et al., 2010)	Can a heart failure-specific cardiac rehabilitation program decrease hospitalizations and improve outcomes in high-risk patients?	Partly unsupervised
(Davies et al., 2010)	Exercise training for systolic heart failure: Cochrane systematic review and meta-analysis.	Not every included article was supervised

(de Meirelles et al., 2014)	Chronic exercise leads to antiaggregant, antioxidant and anti-inflammatory effects in heart failure patients	No hospitalization /mortality
(de Mello Franco et al., 2006)	Effects of home-based exercise training on neurovascular control in patients with heart failure	Unsupervised
(Dieberg, Ismail, Giallauria, & Smart, 2015)	Clinical outcomes and cardiovascular responses to exercise training in heart failure patients with preserved ejection fraction: a systematic review and meta-analysis.	Not every included article was aimed to train physical fitness
(Dracup et al., 2007)	Effects of a home-based exercise program on clinical outcomes in heart failure	Unsupervised
(Duncan et al., 2017)	The comprehensive post-acute stroke services (COMPASS) study: design and methods for a cluster-randomized pragmatic trial	Completion date before 2017/11/01
(Erdman, Duivenvoorden, Verhage, Kazemier, & Hugenholtz, 1986)	Predictability of beneficial effects in cardiac rehabilitation: a randomized clinical trial of psychosocial variables	No prognostic outcome
(Fearon & Langhorne, 2012)	Services for reducing duration of hospital care for acute stroke patients	No training of physical fitness
(Fridlund, Hogstedt, Lidell, & Larsson, 1991)	Recovery after myocardial infarction: effects of a caring rehabilitation program	No full text available
(Fukuta, Goto, Wakami, & Ohte, 2016)	Effects of drug and exercise intervention on functional capacity and quality of life in heart failure with preserved ejection fraction: A meta-analysis of randomized controlled trials.	Not every included article was supervised
(G. R. Reeves et al., 2017)	A novel rehabilitation intervention for older patients with acute decompensated heart failure: The REHAB-HF Pilot Study	Completion date before 2017/11/01
(Garcia-Alamino et al., 2010)	Self-monitoring and self-management of oral anticoagulation	No training of physical fitness
(Gary, Cress, Higgins, Smith, & Dunbar, 2012)	A combined aerobic and resistance exercise program improves physical functional performance in patients with heart failure: a pilot study.	No VO2 peak, mortality or hospitalization
(Giannuzzi, Temporelli, Corra, & Tavazzi, 2003)	Antiremodeling effect of long-term exercise training in patients with stable chronic heart failure	Partly unsupervised
(Goldman et al., 1993)	Mechanism of death in heart failure. The Vasodilator-Heart Failure Trials. The V-HeFT VA Cooperative Studies Group.	Irrelevant intervention
(Gomes-Neto, Saquetto, da Silva e Silva, Conceicao, & Carvalho, 2016)	Impact of Exercise Training in Aerobic Capacity and Pulmonary Function in Children and Adolescents After Congenital Heart Disease Surgery: A Systematic Review with Meta-analysis.	Subjects younger than 18 years
(Gray, Hart, Smith, & Batty, 2010)	What is the predictive value of established risk factors for total and cardiovascular disease mortality when measured before middle age? Pooled analyses of two prospective cohort studies from Scotland	No training of physical fitness
(Grontved & Hu, 2011)	Television viewing and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality: a meta-analysis	No training of physical fitness
(Hansen et al., 2009)	Reduction of cardiovascular event rate: different effects of cardiac rehabilitation in CABG and PCI patients	Partly unsupervised
(Haykowsky et al., 2013)	Meta-analysis of aerobic interval training on exercise capacity and systolic function in patients with heart failure and reduced ejection fractions.	No control group (no exercise intervention)

(Hedback, Perk, Hornblad, & Ohlsson, 2001)	Cardiac rehabilitation after coronary artery bypass surgery: 10-years results on mortality, morbidity and readmissions to hospital	No full text available
(Hoffmann, Ownsworth, Eames, & Shum, 2015)	Evaluation of brief interventions for managing depression and anxiety symptoms during early discharge period after stroke: a pilot randomized controlled trial	Completion date before 2017/11/01
(Jewiss et al., 2016)	The effect of resistance training on clinical outcomes in heart failure: A systematic review and meta-analysis.	Not every included article was supervised
(Jolly et al., 2009)	A randomized trial of the addition of home-based exercise to specialist heart failure nurse care: the Birmingham Rehabilitation Uptake Maximization study for patients with Congestive Heart Failure (BRUM-CHF) study.	No VO_2 peak, mortality or hospitalization
(Jonkman, Westland, Groenwold, Agren, Anguita, et al., 2016)	What Are Effective Program Characteristics of Self-Management Interventions in Patients With Heart Failure? An Individual Patient Data Meta-analysis	Not every included article was aimed to train physical fitness
(Jonkman, Westland, Groenwold, Agren, Atienza, et al., 2016)	Do Self-Management Interventions Work in Patients With Heart Failure? An Individual Patient Data Meta-Analysis	Not every included article was aimed to train physical fitness
(Kadoglou et al., 2017)	Effect of functional electrical stimulation on cardiovascular outcomes in patients with chronic heart failure	Completion date before 2017/11/01
(Kentala, 1972)	Physical fitness and feasibility of physical rehabilitation after myocardial infarction in men of working age	No full text available
(Keteyian et al., 2016)	Variables Measured During Cardiopulmonary Exercise Testing as Predictors of Mortality in Chronic Systolic Heart Failure.	No exercise intervention
(Keteyian, 2011)	Exercise training in congestive heart failure: risk and benefits	Not every included article had a control group
(Ketola, Sipila, & Makela, 2000)	Effectiveness of individual lifestyle interventions in reducing cardiovascular disease and risk factors.	No training of physical fitness
(Kirschner, 2004)	CPM--Continuous Passive Motion: treatment of injured or operated knee-joints using passive movement. A meta-analysis of current literature	No cardiovascular disease
(Koch, Douard, & Broustet, 1992)	The benefit of graded physical exercise in chronic heart failure.	No VO_2 peak, mortality or hospitalization
(Koukouvou et al., 2004)	Quality of life, psychological and physiological changes following exercise training in patients with chronic heart failure	No hospitalization /mortality
(Kovoor et al., 2006)	Return to full normal activities including work at two weeks after acute myocardial infarction	Unsupervised
(LaFontaine, Dabney, Brownson, & Smith, 1994)	The effect of physical activity on all cause mortality compared to cardiovascular mortality: a review of research and recommendations	No training of physical fitness in cardiovascular disease
(Langhorne & Duncan, 2001)	Does the organization of post acute stroke care really matter?	No training of physical fitness
(Larsen, Olsen, & Sorensen, 2006)	Early home-supported discharge of stroke patients: a health technology assessment	No prognostic outcome

(Leemrijse et al., 2016)	The telephone lifestyle intervention 'Hartcoach' has modest impact on coronary risk factors: a randomized multicentre trial	Completion date before 2017/11/01
(Lewinter et al., 2015)	Exercise-based cardiac rehabilitation in patients with heart failure: a meta-analysis of randomized controlled trials between 1999 and 2013	Not every included article was supervised
(Li et al., 2016)	Efficacy of prenatal diagnosis of major congenital heart disease on perinatal management and perioperative mortality: a meta-analysis	No training of physical fitness
(Lidell & Fridlund, 1996)	Long-term effects of a comprehensive rehabilitation programme after myocardial infarction	No full text available
(Loeb et al., 1993)	Effect of enalapril, hydralazine plus isosorbide dinitrate, and prazosin on hospitalization in patients with chronic congestive heart failure. The V-HeFT VA Cooperative Studies Group.	Irrelevant intervention
(Long et al., 2018)	Exercise-based cardiac rehabilitation for adults with stable angina.	Unsupervised
(M. J. Reeves et al., 2017)	Improving transitions in acute stroke patients discharged to home: the Michigan stroke transitions trials (MISTT) protocol	Completion date before 2017/11/01
(Maiorana et al., 2011)	The impact of exercise training on conduit artery wall thickness and remodelling in chronic heart failure patients	No aerobic intervention
(Mandic et al., 2009)	Effects of aerobic or aerobic and resistance training on cardiorespiratory and skeletal muscle function in heart failure: a randomized controlled pilot trial	No hospitalization /mortality
(Maroto Montero, Artigao Ramirez, Morales Duran, de Pablo Zarzosa, & Abraira, 2005)	Cardiac rehabilitation in patients with myocardial infarction: a 10-year follow-up study	Partly unsupervised
(McAlister et al., 2004)	Systematic review: cardiac resynchronization in patients with symptomatic heart failure	No training of physical fitness
(McKelvie et al., 2002)	Effects of exercise training in patients with heart failure: the Exercise Rehabilitation Trial (EXERT).	No VO_2 peak, mortality or hospitalization
(Meenan et al., 2016)	An economic evaluation of a weight loss intervention program for people with serious mental illnesses taking antipsychotic medications	Completion date before 2017/11/01
(Mehani, 2013)	Correlation between changes in diastolic dysfunction and health-related quality of life after cardiac rehabilitation program in dilated cardiomyopathy	No prognostic outcome
(Mentz et al., 2013)	Race, exercise training, and outcomes in chronic heart failure: findings from heart failure - A controlled trial investigating outcomes in exercise training (HF-ACTION)	Partly unsupervised
(Morris et al., 2014)	Association of lower extremity performance with cardiovascular and all-cause mortality in patients with peripheral artery disease: a systematic review and meta-analysis	No training of physical fitness
(N. C. Foley, Teasell, Bhogal, Doherty, & Speechley, 2003)	The efficacy of stroke rehabilitation: a qualitative review	No training of physical fitness
(N. Foley, Salter, & Teasell, 2007)	Specialized stroke services: A meta-analysis comparing three models of care.	No training of physical fitness

(Naci & Ioannidis, 2013)	Comparative effectiveness of exercise and drug interventions on mortality outcomes: meta epidemiological study	Not every included article was supervised
(Nicholl, Coleman, & Brazier, 1994)	Health and healthcare costs and benefits of exercise	No training of physical fitness in cardiovascular disease
(Nielsen, Faergeman, Foldspang, & Larsen, 2008)	Cardiac rehabilitation: health characteristics and socio-economic status among those who do not attend	No control group
(Nikolaus & Jamour, 2000)	Effectiveness of special stroke units in treatment of acute stroke	No training of physical fitness
(O'Connor et al., 2009)	Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial	Partly unsupervised
(Oka et al., 2000)	Impact of a home-based walking and resistance training program on quality of life in patients with heart failure	No supervision
(Oldridge, 2012)	Exercise-based cardiac rehabilitation in patients with coronary heart disease: meta-analysis outcomes revisited	Not every included article was supervised
(Or, Tao, & Wang, 2017)	The effectiveness of the use of consumer health information technology in patients with heart failure: A meta-analysis and narrative review of randomized controlled trials	No training of physical fitness
(Palazzuoli et al., 2006)	Erythropoietin improves anemia exercise tolerance and renal function and reduces B-type natriuretic peptide and hospitalization in patients with heart failure and anemia.	Irrelevant intervention
(Pang, Eng, Dawson, & Gylfadottir, 2006)	The use of aerobic exercise training in improving aerobic capacity in individuals with stroke: a meta-analysis.	No control group (no exercise intervention)
(Parikh et al., 2016)	Relation of Angina Pectoris to Outcomes, Quality of Life and Response to Exercise Training in Patients with Chronic Heart Failure (from HF-ACTION)	Partly unsupervised
(Park et al., 2017)	Symptom diary use and improved survival for patients with heart failure	No supervision
(Parmenter, Dieberg, & Smart, 2015)	Exercise training for management of peripheral arterial disease: a systematic review and meta-analysis.	Not every included article was supervised
(Pina et al., 2014)	Effects of exercise training on outcomes in women with heart failure: analysis of HF-ACTION (Heart Failure-A Controlled Trial Investigating Outcomes of Exercise TraiNing) by sex.	Partly unsupervised
(Ponikowski et al., 2007)	Effect of darbepoetin alfa on exercise tolerance in anemic patients with symptomatic chronic heart failure: a randomized, double-blind, placebo-controlled trial.	Irrelevant intervention
(Prescher et al., 2016)	Prognostic value of serial six-minute walk tests using tele-accelerometry in patients with chronic heart failure: a prespecified sub-study of the TIM-HF-Trial	Completion date before 2017/11/01
(Prince, Blanchard, Grace, & Reid, 2016)	Objectively-measured sedentary time and its association with markers of cardiometabolic health and fitness among cardiac rehabilitation graduates	Completion date before 2017/11/01
(Reid et al., 2012)	Exercise prescription for hospitalized people with chronic obstructive pulmonary disease and comorbidities: a synthesis of systematic reviews	No cardiovascular disease
(Reimers, Knapp, & Reimers, 2009)	Exercise as stroke prophylaxis	No training of physical fitness

(S. H. Lo, Chang, & Chau, 2016)	Study protocol: a randomised controlled trial of a nurse-led community based self-management programme for improving recovery among community-residing stroke survivors	Completion date before 2017/11/01
(S. H. S. Lo, Chang, & Chau, 2018)	Stroke self-management support improves survivors' self-efficacy and outcome expectation of self-management behaviours	No supervision
(Sabelis et al., 2004)	Does physical training increase insulin sensitivity in chronic heart failure patients?	No VO_2 peak, mortality or hospitalization
(Santaularia et al., 2017)	The efficacy of a supervised exercise training programme on readmission rates in patients with myocardial ischemia: results from a randomised controlled trial	Completion date before 2017/11/01
(Sbruzzi et al., 2010)	Functional electrical stimulation in the treatment of patients with chronic heart failure: a meta-analysis of randomized controlled trials.	Irrelevant intervention
(Schuler et al., 1992)	Regular physical exercise and low-fat diet: effects on progression of coronary artery disease	Partly unsupervised
(Selig et al., 2004)	Moderate-intensity resistance exercise training in patients with chronic heart failure improves strength, endurance, heart rate variability, and forearm blood flow.	No VO2 peak, mortality or hospitalization
(Servantes et al., 2012)	Effects of home-based exercise training for patients with chronic heart failure and sleep apnoe: a randomized comparison of two different programs	No supervision
(Shepherd et al., 2017)	Combined diet and exercise interventions for preventing gestational diabetes mellitus	No cardiovascular disease
(Sivarajan et al., 1982)	Treadmill test responses to an early exercise program after myocardial infarction: a randomized study	Partly unsupervised
(Smart, Dieberg, & Giallauria, 2013)	Functional electrical stimulation for chronic heart failure: a meta-analysis.	Irrelevant intervention
(Smith, Arthur, McKelvie, & Kodis, 2004)	Differences in sustainability of exercise and health-related quality of life outcomes following home or hospital-based cardiac rehabilitation.	Partly unsupervised
(Snowdon, Haines, & Skinner, 2014)	Preoperative intervention reduces postoperative pulmonary complications but not length of stay in cardiac surgical patients: a systematic review	Most included articles did not aim to train physical fitness
(Swank et al., 2012)	Modest increase in peak VO2 is related to better clinical outcomes in chronic heart failure patients: results from heart failure and a controlled trial to investigate outcomes of exercise training (HF-ACTION)	Partly unsupervised
(Tay, Tan, Diener, & Gonzalez, 2013)	Social relations, health behaviours, and health outcomes: a survey and synthesis	No training of physical fitness
(Taylor et al., 2014)	Exercise-based rehabilitation for heart failure	Not every included article was supervised
(Teasell, Foley, Bhogal, & Speechley, 2003)	Early supported discharge in stroke rehabilitation	No prognostic outcome
(Toot, Devine, Akporobaro, & Orrell, 2013)	Causes of hospital admission for people with dementia: a systematic review and meta-analysis	No cardiovascular disease
(Tyni-Lenne, Dencker, Gordon, Jansson, & Sylven, 2001)	Comprehensive local muscle training increases aerobic working capacity and quality of life and decreases neurohormonal activation in patients with chronic heart failure.	No VO_2 peak, mortality or hospitalization

(van Halewijn et al., 2017)	Lessons from contemporary trials of cardiovascular prevention and rehabilitation: A systematic review and meta-analysis	Not every included article aimed to train physical fitness
(Vancampfort et al., 2015)	Promotion of cardiorespiratory fitness in schizophrenia: a clinical overview and meta-analysis.	No cardiovascular disease
(Weight cycling("Weight cycling. National Task Force on the Prevention and Treatment of Obesity," 1994)	Weight cycling. National Task Force on the Prevention and Treatment of Obesity	No cardiovascular disease
(Williams et al., 2007)	Circuit resistance training in chronic heart failure improves skeletal muscle mitochondrial ATP production rate--a randomized controlled trial.	No aerobic training
(Winslow, Lane, & Gaffney, 1985)	Oxygen uptake and cardiovascular responses in control adults and acute myocardial infarction patients during bathing.	Irrelevant intervention
(Witham et al., 2005)	Effect of a seated exercise program to improve physical function and health status in frail patients > or = 70 years of age with heart failure.	No VO_2 peak, mortality or hospitalization
(Xie, Yan, Cai, & Li, 2017)	Effects of high-intensity interval training on aerobic capacity in cardiac patients: a systematic review with meta-analysis.	No control group (no exercise intervention)
(Y. Chen et al., 2018)	Effectiveness of a multidisciplinary disease management program on outcomes in patients with heart failure in China: a randomized controlled single centre study	No supervision
(Y. W. Chen et al., 2018)	Home-based cardiac rehabilitation improves quality of life, aerobic capacity, and readmission rates in patients with chronic heart failure	No supervision
(Yu et al., 2004)	A short course of cardiac rehabilitation program is highly cost effective in improving long-term quality of life in patients with recent myocardial infarction or percutaneous coronary intervention (Yu 2004)	No prognostic outcome
(Zeng et al., 2013)	Benefits and costs of intensive lifestyle modification programs for symptomatic coronary disease in Medicare beneficiaries (Zeng 2013)	No control group
(Zhu, Lee, & Chee, 2012)	Fast-track cardiac care for adult cardiac surgical patients	No training of physical fitness
(Zick, Vautaw, Gillespie, & Aaronson, 2009)	Hawthorn Extract Randomized Blinded Chronic Heart Failure (HERB CHF) trial.	Unsupervised

Table 7: Quality assessment

Table 7.1 Quality assessment of systematic reviews and meta-analyses.

Author	(Zhang et al., 2016)	
Meta-analysis or systematic review?	Meta-analysis	
Topic	Question	Yes/No/ Not applicable
Title		
Title	Is the title of the study mentioned?	Yes (1)
Abstract		
Structured summary	Does the article have a structured summary? This summary includes: background, objectives, study eligibility criteria, participants, interventions, study appraisal, results and conclusion.	Yes (1)
Introduction		
Rationale	Is the motivation of this systematic review or meta-analysis mentioned? And is this derived from what is already known?	Yes (1)
Objectives	Is there a clear research question mentioning patients, interventions, outcomes?	Yes (1)
	Is there an explanation why they choose these particular patients, interventions and outcomes?	Yes (1)
Methods		
Protocol and registration	Is there a review protocol? If it is present, is the registration number mentioned?	No (0)
Eligibility criteria	Are there inclusion and exclusion criteria used to recruit the articles?	Yes (1)
Information source	Are the information sources mentioned?	Yes (1)
Search	Is the search strategy of at least one database mentioned in the article, so it can be searched in the same way?	Yes (1)
Study selection	Is the process of how the studies were selected mentioned in the article? (Screening, inclusion/exclusion)	Yes (1)
Data collection process	Is the data extraction process described?	Yes (1)
Synthesis of results	Are the results of the individual studies combined in this study?	Yes (1)
Additional analyses	Have additional analyses been carried out (e.g. subgroup analyses, meta-regression)?	Not applicable
Results		
Study selection	Is the number of screened studies and the reason for exclusion mentioned in each phase of study selection?	Yes (1)
Study characteristics	Are the study characteristics (PICO, study size, follow-up period) of all the studies that were included, mentioned in the article?	Yes (1)
Risk of bias in at least one study	Is there a risk of selection bias?	No (1)
	Is there a risk of performance bias?	Yes (0)

	Is there a risk of attrition bias?	No (1)
Synthesis of results	Are the results described, including the confidence intervals and measures of consistency?	Yes (1)
Additional analysis	Are the results of additional analysis mentioned (only if there was additional analysis carried out)?	Not applicable
Discussion		
Summary of evidence	Is the strength of evidence, such as effect size, mentioned for each outcome for the main findings?	No (0)
Limitations	Are the limitations of the study and outcomes mentioned?	Yes (1)
Conclusions	Is there a general conclusion been made?	Yes (1)
	Are there any recommendations mentioned for future research?	Yes (1)
Funding		
Funding	Are the sources of funding described?	Yes (1)
Total score	1 = positive, 0 = negative, irrelevant = not applicable	20/23

Author	(Gomes Neto et al., 2014)	
meta-analysis or systematic review?	Meta-analysis	
Topic	Question	Yes/No/ Not applicable
Title		
Title	Is the title of the study mentioned?	Yes (1)
Abstract		
Structured summary	Does the article have a structured summary? This summary includes: background, objectives, study eligibility criteria, participants, interventions, study appraisal, results and conclusion.	Yes (1)
Introduction		
Rationale	Is the motivation of this systematic review or meta-analysis mentioned? And is this derived from what is already known?	Yes (1)
Objectives	Is there a clear research question mentioning patients, interventions, outcomes?	No (0)
	Is there an explanation why they choose these particular patients, interventions and outcomes?	Yes (1)
Methods		
Protocol and registration	Is there a review protocol? If it is present, is the registration number mentioned?	No (0)
Eligibility criteria	Are there inclusion and exclusion criteria used to recruit the articles?	Yes (1)
Information source	Are the information sources mentioned?	Yes (1)
Search	Is the search strategy of at least one database mentioned in the article, so it can be searched in the same way?	No (0)
Study selection	Is the process of how the studies were selected mentioned in the article? (Screening, inclusion/exclusion)	No (0)

Data collection process	Is the data extraction process described?	Yes (1)
Synthesis of results	Are the results of the individual studies combined in this study?	Yes (1)
Additional analyses	Have additional analyses been carried out (e.g. subgroup analyses, meta-regression)?	Not applicable
Results		
Study selection	Is the number of screened studies and the reason for exclusion mentioned in each phase of study selection?	No (0)
Study characteristics	Are the study characteristics (PICO, study size, follow-up period) of all the studies that were included, mentioned in the article?	Yes (1)
Risk of bias in at least one study	Is there a risk of selection bias?	No (1)
	Is there a risk of performance bias?	Yes (0)
	Is there a risk of attrition bias?	No (1)
Synthesis of results	Are the results described, including the confidence intervals and measures of consistency?	Yes (1)
Additional analysis	Are the results of additional analysis mentioned (only if there was additional analysis carried out)?	Not applicable
Discussion		
Summary of evidence	Is the strength of evidence, such as effect size, mentioned for each outcome for the main findings?	No (0)
Limitations	Are the limitations of the study and outcomes mentioned?	Yes (1)
Conclusions	Is there a general conclusion been made?	Yes (1)
	Are there any recommendations mentioned for future research?	Yes (1)
Funding		
Funding	Are the sources of funding described?	Yes (1)
Total score	1 = positive, 0 = negative, irrelevant = not applicable	16/23

Author	(Ismail et al., 2013)	
meta-analysis or systematic review?	Meta-analysis	
Topic	Question	Yes/No/ Not applicable
Title		
Title	Is the title of the study mentioned?	Yes (1)
Abstract		
Structured summary	Does the article have a structured summary? This summary includes: background, objectives, study eligibility criteria, participants, interventions, study appraisal, results and conclusion.	Yes (1)
Introduction		
Rationale	Is the motivation of this systematic review or meta-analysis mentioned? And is this derived from what is already known?	Yes (1)

Objectives	Is there a clear research question mentioning patients, interventions, outcomes?	Yes (1)
	Is there an explanation why they choose these particular patients, interventions and outcomes?	Yes (1)
Methods		
Protocol and registration	Is there a review protocol? If it is present, is the registration number mentioned?	No (0)
Eligibility criteria	Are there inclusion and exclusion criteria used to recruit the articles?	Yes (1)
Information source	Are the information sources mentioned?	Yes (1)
Search	Is the search strategy of at least one database mentioned in the article, so it can be searched in the same way?	Yes (1)
Study selection	Is the process of how the studies were selected mentioned in the article? (Screening, inclusion/exclusion)	Yes (1)
Data collection process	Is the data extraction process described?	Yes (1)
Synthesis of results	Are the results of the individual studies combined in this study?	Yes (1)
Additional analyses	Have additional analyses been carried out (e.g. subgroup analyses, meta-regression)?	Yes (1)
Results		
Study selection	Is the number of screened studies and the reason for exclusion mentioned in each phase of study selection?	Yes (1)
Study characteristics	Are the study characteristics (PICO, study size, follow-up period) of all the studies that were included, mentioned in the article?	Yes (1)
Risk of bias in at least one study	Is there a risk of selection bias?	No (1)
	Is there a risk of performance bias?	Yes (0)
	Is there a risk of attrition bias?	No (1)
Synthesis of results	Are the results described, including the confidence intervals and measures of consistency?	Yes (1)
Additional analysis	Are the results of additional analysis mentioned (only if there was additional analysis carried out)?	Yes (1)
Discussion		
Summary of evidence	Is the strength of evidence, such as effect size, mentioned for each outcome for the main findings?	No (0)
Limitations	Are the limitations of the study and outcomes mentioned?	Yes (1)
Conclusions	Is there a general conclusion been made?	Yes (1)
	Are there any recommendations mentioned for future research?	No (0)
Funding		
Funding	Are the sources of funding described?	No (0)
Total score	1 = positive, 0 = negative, irrelevant = not applicable	20/25

Author	(Ismail et al., 2014)	
meta-analysis or systematic review?	Meta-analysis	
Topic	Question	Yes/No/ Not applicable
Title		
Title	Is the title of the study mentioned?	Yes (1)
Abstract		
Structured summary	Does the article have a structured summary? This summary includes: background, objectives, study eligibility criteria, participants, interventions, study appraisal, results and conclusion.	Yes (1)
Introduction		
Rationale	Is the motivation of this systematic review or meta-analysis mentioned? And is this derived from what is already known?	Yes (1)
Objectives	Is there a clear research question mentioning patients, interventions, outcomes?	Yes (1)
	Is there an explanation why they choose these particular patients, interventions and outcomes?	Yes (1)
Methods		
Protocol and registration	Is there a review protocol? If it is present, is the registration number mentioned?	No (0)
Eligibility criteria	Are there inclusion and exclusion criteria used to recruit the articles?	Yes (1)
Information source	Are the information sources mentioned?	Yes (1)
Search	Is the search strategy of at least one database mentioned in the article, so it can be searched in the same way?	Yes (1)
Study selection	Is the process of how the studies were selected mentioned in the article? (Screening, inclusion/exclusion)	Yes (1)
Data collection process	Is the data extraction process described?	Yes (1)
Synthesis of results	Are the results of the individual studies combined in this study?	Yes (1)
Additional analyses	Have additional analyses been carried out (e.g. subgroup analyses, meta-regression)?	Not applicable
Results		
Study selection	Is the number of screened studies and the reason for exclusion mentioned in each phase of study selection?	Yes (1)
Study characteristics	Are the study characteristics (PICO, study size, follow-up period) of all the studies that were included, mentioned in the article?	Yes (1)
Risk of bias in at least one study	Is there a risk of selection bias?	No (1)
	Is there a risk of performance bias?	Yes (0)
	Is there a risk of attrition bias?	No (1)
Synthesis of results	Are the results described, including the confidence intervals and measures of consistency?	Yes (1)

Additional analysis	Are the results of additional analysis mentioned (only if there was additional analysis carried out)?	Not applicable
Discussion		
Summary of evidence	Is the strength of evidence, such as effect size, mentioned for each outcome for the main findings?	No (0)
Limitations	Are the limitations of the study and outcomes mentioned?	Yes (1)
Conclusions	Is there a general conclusion been made?	Yes (1)
	Are there any recommendations mentioned for future research?	No (0)
Funding		
Funding	Are the sources of funding described?	No (0)
Total score	1 = positive, 0 = negative, irrelevant = not applicable	18/23

Author	(Smart et al., 2012)	
meta-analysis or systematic review?	Meta-analysis	
Topic	Question	Yes/No/ Not applicable
Title		
Title	Is the title of the study mentioned?	Yes (1)
Abstract		
Structured summary	Does the article have a structured summary? This summary includes: background, objectives, study eligibility criteria, participants, interventions, study appraisal, results and conclusion.	Yes (1)
Introduction		
Rationale	Is the motivation of this systematic review or meta-analysis mentioned? And is this derived from what is already known?	Yes (1)
Objectives	Is there a clear research question mentioning patients, interventions, outcomes?	Yes (1)
	Is there an explanation why they choose these particular patients, interventions and outcomes?	Yes (1)
Methods		
Protocol and registration	Is there a review protocol? If it is present, is the registration number mentioned?	No (0)
Eligibility criteria	Are there inclusion and exclusion criteria used to recruit the articles?	Yes (1)
Information source	Are the information sources mentioned?	Yes (1)
Search	Is the search strategy of at least one database mentioned in the article, so it can be searched in the same way?	No (0)
Study selection	Is the process of how the studies were selected mentioned in the article? (Screening, inclusion/exclusion)	Yes (1)
Data collection process	Is the data extraction process described?	Yes (1)
Synthesis of results	Are the results of the individual studies combined in this study?	Yes (1)

Additional analyses	Have additional analyses been carried out (e.g. subgroup analyses, meta-regression)?	Yes (1)
Results		
Study selection	Is the number of screened studies and the reason for exclusion mentioned in each phase of study selection?	Yes (1)
Study characteristics	Are the study characteristics (PICO, study size, follow-up period) of all the studies that were included, mentioned in the article?	No (0)
Risk of bias in at least one study	Is there a risk of selection bias?	No (1)
	Is there a risk of performance bias?	Yes (0)
	Is there a risk of attrition bias?	No (1)
Synthesis of results	Are the results described, including the confidence intervals and measures of consistency?	Yes (1)
Additional analysis	Are the results of additional analysis mentioned (only if there was additional analysis carried out)?	Yes (1)
Discussion		
Summary of evidence	Is the strength of evidence, such as effect size, mentioned for each outcome for the main findings?	No (0)
Limitations	Are the limitations of the study and outcomes mentioned?	No (0)
Conclusions	Is there a general conclusion been made?	Yes (1)
	Are there any recommendations mentioned for future research?	Yes (1)
Funding		
Funding	Are the sources of funding described?	Yes (1)
Total score	1 = positive, 0 = negative, irrelevant = not applicable	19/25

Table 7.2: Quality assessment of Randomized Controlled Trials

Author	(Briffa et al., 2005)	
Topic	Checklist item	Reported on page number
Title and abstract		
	Identification as a randomized trial in the title	450
	Structured summary of trial design, methods, results and conclusions	450
Introduction		
Background and objectives	Specific background and explanation of rationale	450
	Specific objectives or hypotheses	450
Methods		
Trial design	Description of trial design (such as parallel, factorial) including allocation ratio	450-451
	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Not applicable
Participants	Eligibility criteria for participants	450
	Setting and locations where the data were collected	450-451
Interventions	The interventions for each group with sufficient details allow replication, including how and when they were actually administered	451
Outcomes	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	451-452
	Any changes to trial outcomes after the trial commenced, with reasons	Not applicable
Sample size	How sample size was determined	452-453
	When applicable, explanation of any interim analyses and stopping guidelines	Not applicable
Randomization (method)		
Sequence generation	Method used to generate the random allocation sequence	450-451
	Type of randomization; details of any restriction (such as blocking and block size)	450-451
Allocation concealment mechanism	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taking to conceal the sequence until interventions were assigned	450-451
Implementation	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	450-451
Blinding	If done, who blinded after assignment to interventions (for example participants, care providers, those assessing outcomes- and how	Score = 0
	If relevant, description of the similarity of interventions	451
Statistical methods	Statistical methods used to compare groups for primary and secondary outcomes	452
	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Not applicable
Results		
Participant flow	For each group, the number of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	452-453
	For Each group, losses, and exclusions after randomization, together with reasons	452-453
Recruitment	Dates defining the periods of recruitment and follow-up	Score = 0
	Why the trial ended or stopped	453
Baseline data	A table showing baseline demographic and clinical characteristics for each group	452

Numbers analyzed	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	453
Outcomes and estimation	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	453-454
	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable
Ancillary analyses	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	454
Harms	All important harms or unintended effects in each group	Not applicable
Discussion		
Limitations	Trial limitations, addressing sources of potential bias, impressions, and, if relevant, multiplicity of analyses	454-455
Generalizability	Generalizability (external validity, applicability of the trial findings	Score = 0
Interpretation	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	454-455
Other information		
Registration	Registration number and name of trial registry	Score = 0
Protocol	Where the full trial protocol can be accessed, if available	Not applicable
Funding	Sources of funding and other support (such as supply of drugs), role of funders	Score = 0
Total score	Page number = 1, not mentioned = 0, irrelevant = not applicable	27/30

Author	(Dendale et al., 2005)	
Topic	Checklist item	Reported on page number
Title and abstract		
	Identification as a randomized trial in the title	Score = 0
	Structured summary of trial design, methods, results and conclusions	113
Introduction		
Background and objectives	Specific background and explanation of rationale	113-114
	Specific objectives or hypotheses	113
Methods		
Trial design	Description of trial design (such as parallel, factorial) including allocation ratio	114
	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Not applicable
Participants	Eligibility criteria for participants	114
	Setting and locations where the data were collected	114
Interventions	The interventions for each group with sufficient details allow replication, including how and when they were actually administered	114
Outcomes	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	114
	Any changes to trial outcomes after the trial commenced, with reasons	Not applicable
Sample size	How sample size was determined	114
	When applicable, explanation of any interim analyses and stopping guidelines	114-115

Randomization (method)		
Sequence generation	Method used to generate the random allocation sequence	Not applicable
	Type of randomization; details of any restriction (such as blocking and block size)	Not applicable
Allocation concealment mechanism	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taking to conceal the sequence until interventions were assigned	Not applicable
Implementation	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	114
Blinding	If done, who blinded after assignment to interventions (for example participants, care providers, those assessing outcomes- and how	Not applicable
	If relevant, description of the similarity of interventions	Not applicable
Statistical methods	Statistical methods used to compare groups for primary and secondary outcomes	114-115
	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Not applicable
Results		
Participant flow	For each group, the number of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	115
	For Each group, losses, and exclusions after randomization, together with reasons	115
Recruitment	Dates defining the periods of recruitment and follow-up	Score = 0
	Why the trial ended or stopped	114
Baseline data	A table showing baseline demographic and clinical characteristics for each group	Score = 0
Numbers analyzed	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	115
Outcomes and estimation	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	114-115
	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable
Ancillary analyses	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Not applicable
Harms	All important harms or unintended effects in each group	Not applicable
Discussion		
Limitations	Trial limitations, addressing sources of potential bias, impressions, and, if relevant, multiplicity of analyses	116
Generalizability	Generalizability (external validity, applicability of the trial findings	Score = 0
Interpretation	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	115-116
Other information		
Registration	Registration number and name of trial registry	Score = 0
Protocol	Where the full trial protocol can be accessed, if available	Not applicable
Funding	Sources of funding and other support (such as supply of drugs), role of funders	Score = 0
Total score	Page number = 1, not mentioned = 0, irrelevant = not applicable	19/25

Author	(Dendale et al., 2008)	
Topic	Checklist item	Reported on page number
Title and abstract		
	Identification as a randomized trial in the title	Not applicable
	Structured summary of trial design, methods, results and conclusions	451
Introduction		
Background and objectives	Specific background and explanation of rationale	451-452
	Specific objectives or hypotheses	451-452
Methods		
Trial design	Description of trial design (such as parallel, factorial) including allocation ratio	452
	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Not applicable
Participants	Eligibility criteria for participants	452
	Setting and locations where the data were collected	452
Interventions	The interventions for each group with sufficient details allow replication, including how and when they were actually administered	452
Outcomes	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	452
	Any changes to trial outcomes after the trial commenced, with reasons	Not applicable
Sample size	How sample size was determined	452
	When applicable, explanation of any interim analyses and stopping guidelines	Not applicable
Randomization (method)		
Sequence generation	Method used to generate the random allocation sequence	Not applicable
	Type of randomization; details of any restriction (such as blocking and block size)	Not applicable
Allocation concealment mechanism	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taking to conceal the sequence until interventions were assigned	Not applicable
Implementation	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	452
Blinding	If done, who blinded after assignment to interventions (for example participants, care providers, those assessing outcomes- and how	Not applicable
	If relevant, description of the similarity of interventions	Not applicable
Statistical methods	Statistical methods used to compare groups for primary and secondary outcomes	453
	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Not applicable
Results		
Participant flow	For each group, the number of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	453
	For Each group, losses, and exclusions after randomization, together with reasons	453
Recruitment	Dates defining the periods of recruitment and follow-up	Not applicable
	Why the trial ended or stopped	Not applicable
Baseline data	A table showing baseline demographic and clinical characteristics for each group	453

Numbers analyzed	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	453
Outcomes and estimation	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	453-454
	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable
Ancillary analyses	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Not applicable
Harms	All important harms or unintended effects in each group	Not applicable
Discussion		
Limitations	Trial limitations, addressing sources of potential bias, impressions, and, if relevant, multiplicity of analyses	454-455
Generalizability	Generalizability (external validity, applicability of the trial findings	Not applicable
Interpretation	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	454-455
Other information		
Registration	Registration number and name of trial registry	Not applicable
Protocol	Where the full trial protocol can be accessed, if available	Not applicable
Funding	Sources of funding and other support (such as supply of drugs), role of funders	Not applicable
Total score	Page number = 1, not mentioned = 0, irrelevant = not applicable	18/24

Author	(Denollet & Brutsaert, 2001)	
Topic	Checklist item	Reported on page number
Title and abstract		
	Identification as a randomized trial in the title	Not applicable
	Structured summary of trial design, methods, results and conclusions	2018
Introduction		
Background and objectives	Specific background and explanation of rationale	2018
	Specific objectives or hypotheses	2018
Methods		
Trial design	Description of trial design (such as parallel, factorial) including allocation ratio	2019
	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Not applicable
Participants	Eligibility criteria for participants	2019
	Setting and locations where the data were collected	2019
Interventions	The interventions for each group with sufficient details allow replication, including how and when they were actually administered	2019
Outcomes	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	2019
	Any changes to trial outcomes after the trial commenced, with reasons	Not applicable
Sample size	How sample size was determined	2019
	When applicable, explanation of any interim analyses and stopping guidelines	Not applicable

Randomization (method)		
Sequence generation	Method used to generate the random allocation sequence	Not applicable
	Type of randomization; details of any restriction (such as blocking and block size)	Not applicable
Allocation concealment mechanism	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taking to conceal the sequence until interventions were assigned	Not applicable
Implementation	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	2019
Blinding	If done, who blinded after assignment to interventions (for example participants, care providers, those assessing outcomes- and how	Not applicable
	If relevant, description of the similarity of interventions	Not applicable
Statistical methods	Statistical methods used to compare groups for primary and secondary outcomes	2019
	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Not applicable
Results		
Participant flow	For each group, the number of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	2019
	For Each group, losses, and exclusions after randomization, together with reasons	2019
Recruitment	Dates defining the periods of recruitment and follow-up	Not applicable
	Why the trial ended or stopped	Not applicable
Baseline data	A table showing baseline demographic and clinical characteristics for each group	2020
Numbers analyzed	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	2020
Outcomes and estimation	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Not applicable
	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable
Ancillary analyses	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Not applicable
Harms	All important harms or unintended effects in each group	Not applicable
Discussion		
Limitations	Trial limitations, addressing sources of potential bias, impressions, and, if relevant, multiplicity of analyses	2021-2022
Generalizability	Generalizability (external validity, applicability of the trial findings	Not applicable
Interpretation	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	2021-2022
Other information		
Registration	Registration number and name of trial registry	Not applicable
Protocol	Where the full trial protocol can be accessed, if available	Not applicable
Funding	Sources of funding and other support (such as supply of drugs), role of funders	Not applicable
Total score	Page number = 1, not mentioned = 0, irrelevant = not applicable	17/24

Author	(La Rovere et al., 2002)	
Topic	Checklist item	Reported on page number
Title and abstract		
	Identification as a randomized trial in the title	Not applicable
	Structured summary of trial design, methods, results and conclusions	945
Introduction		
Background and objectives	Specific background and explanation of rationale	945
	Specific objectives or hypotheses	945
Methods		
Trial design	Description of trial design (such as parallel, factorial) including allocation ratio	945-946
	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Not applicable
Participants	Eligibility criteria for participants	945-946
	Setting and locations where the data were collected	945-946
Interventions	The interventions for each group with sufficient details allow replication, including how and when they were actually administered	946
Outcomes	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	946
	Any changes to trial outcomes after the trial commenced, with reasons	Not applicable
Sample size	How sample size was determined	946
	When applicable, explanation of any interim analyses and stopping guidelines	Not applicable
Randomization (method)		
Sequence generation	Method used to generate the random allocation sequence	945-946
	Type of randomization; details of any restriction (such as blocking and block size)	946
Allocation concealment mechanism	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taking to conceal the sequence until interventions were assigned	Not applicable
Implementation	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Not applicable
Blinding	If done, who blinded after assignment to interventions (for example participants, care providers, those assessing outcomes- and how	Not applicable
	If relevant, description of the similarity of interventions	Not applicable
Statistical methods	Statistical methods used to compare groups for primary and secondary outcomes	946
	Methods for additional analyses, such as subgroup analyses and adjusted analyses	946
Results		
Participant flow	For each group, the number of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	946
	For Each group, losses, and exclusions after randomization, together with reasons	Not applicable
Recruitment	Dates defining the periods of recruitment and follow-up	Not applicable
	Why the trial ended or stopped	Not applicable
Baseline data	A table showing baseline demographic and clinical characteristics for each group	946

Numbers analyzed	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	946
Outcomes and estimation	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	946-947
	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable
Ancillary analyses	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	947
Harms	All important harms or unintended effects in each group	Not applicable
Discussion		
Limitations	Trial limitations, addressing sources of potential bias, impressions, and, if relevant, multiplicity of analyses	947-948
Generalizability	Generalizability (external validity, applicability of the trial findings	948
Interpretation	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	947-949
Other information		
Registration	Registration number and name of trial registry	Not applicable
Protocol	Where the full trial protocol can be accessed, if available	Not applicable
Funding	Sources of funding and other support (such as supply of drugs), role of funders	Not applicable
Total score	Page number = 1, not mentioned = 0, irrelevant = not applicable	21/27

Author	(Oldridge et al., 1991)	
Topic	Checklist item	Reported on page number
Title and abstract		
	Identification as a randomized trial in the title	Not applicable
	Structured summary of trial design, methods, results and conclusions	1084
Introduction		
Background and objectives	Specific background and explanation of rationale	1084
	Specific objectives or hypotheses	1084-1085
Methods		
Trial design	Description of trial design (such as parallel, factorial) including allocation ratio	1085
	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Not applicable
Participants	Eligibility criteria for participants	1085
	Setting and locations where the data were collected	1085
Interventions	The interventions for each group with sufficient details allow replication, including how and when they were actually administered	1085
Outcomes	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	1085-1086
	Any changes to trial outcomes after the trial commenced, with reasons	Not applicable
Sample size	How sample size was determined	1085
	When applicable, explanation of any interim analyses and stopping guidelines	Not applicable

Randomization (method)		
Sequence generation	Method used to generate the random allocation sequence	1086-1087
	Type of randomization; details of any restriction (such as blocking and block size)	1086-1087
Allocation concealment mechanism	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taking to conceal the sequence until interventions were assigned	Not applicable
Implementation	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Not applicable
Blinding	If done, who blinded after assignment to interventions (for example participants, care providers, those assessing outcomes- and how	Not applicable
	If relevant, description of the similarity of interventions	Not applicable
Statistical methods	Statistical methods used to compare groups for primary and secondary outcomes	1086
	Methods for additional analyses, such as subgroup analyses and adjusted analyses	1086
Results		
Participant flow	For each group, the number of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	1086-1087
	For Each group, losses, and exclusions after randomization, together with reasons	1086
Recruitment	Dates defining the periods of recruitment and follow-up	Not applicable
	Why the trial ended or stopped	Not applicable
Baseline data	A table showing baseline demographic and clinical characteristics for each group	1087
Numbers analyzed	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	1086-1087
Outcomes and estimation	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	1087-1088
	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable
Ancillary analyses	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	1087-1088
Harms	All important harms or unintended effects in each group	Not applicable
Discussion		
Limitations	Trial limitations, addressing sources of potential bias, impressions, and, if relevant, multiplicity of analyses	1088
Generalizability	Generalizability (external validity, applicability of the trial findings	Not applicable
Interpretation	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	1088
Other information		
Registration	Registration number and name of trial registry	Not applicable
Protocol	Where the full trial protocol can be accessed, if available	Not applicable
Funding	Sources of funding and other support (such as supply of drugs), role of funders	Not applicable
Total score	Page number = 1, not mentioned = 0, irrelevant = not applicable	21/27

Author	(West et al., 2012)	
Topic	Checklist item	Reported on page number
Title and abstract		
	Identification as a randomized trial in the title	637
	Structured summary of trial design, methods, results and conclusions	637
Introduction		
Background and objectives	Specific background and explanation of rationale	637-638
	Specific objectives or hypotheses	637
Methods		
Trial design	Description of trial design (such as parallel, factorial) including allocation ratio	638
	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Not applicable
Participants	Eligibility criteria for participants	638
	Setting and locations where the data were collected	638
Interventions	The interventions for each group with sufficient details allow replication, including how and when they were actually administered	638
Outcomes	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	638-639
	Any changes to trial outcomes after the trial commenced, with reasons	Not applicable
Sample size	How sample size was determined	639
	When applicable, explanation of any interim analyses and stopping guidelines	
Randomization (method)		
Sequence generation	Method used to generate the random allocation sequence	638
	Type of randomization; details of any restriction (such as blocking and block size)	638
Allocation concealment mechanism	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taking to conceal the sequence until interventions were assigned	638
Implementation	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Not applicable
Blinding	If done, who blinded after assignment to interventions (for example participants, care providers, those assessing outcomes- and how	638-639
	If relevant, description of the similarity of interventions	Not applicable
Statistical methods	Statistical methods used to compare groups for primary and secondary outcomes	639
	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Not applicable
Results		
Participant flow	For each group, the number of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	639
	For Each group, losses, and exclusions after randomization, together with reasons	640-641
Recruitment	Dates defining the periods of recruitment and follow-up	Not applicable
	Why the trial ended or stopped	Not applicable
Baseline data	A table showing baseline demographic and clinical characteristics for each group	640

Numbers analyzed	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	639
Outcomes and estimation	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	639-640
	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable
Ancillary analyses	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Not applicable
Harms	All important harms or unintended effects in each group	Not applicable
Discussion		
Limitations	Trial limitations, addressing sources of potential bias, impressions, and, if relevant, multiplicity of analyses	642-643
generalizability	Generalizability (external validity, applicability of the trial findings	Not applicable
Interpretation	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	642-643
Other information		
Registration	Registration number and name of trial registry	Not applicable
Protocol	Where the full trial protocol can be accessed, if available	Not applicable
Funding	Sources of funding and other support (such as supply of drugs), role of funders	643
Total score	Page number = 1, not mentioned = 0, irrelevant = not applicable	24/29

Author	(Zwisler et al., 2008)	
Topic	Checklist item	Reported on page number
Title and abstract		
	Identification as a randomized trial in the title	1106
	Structured summary of trial design, methods, results and conclusions	1106
Introduction		
Background and objectives	Specific background and explanation of rationale	1106-1107
	Specific objectives or hypotheses	1107-1108
Methods		
Trial design	Description of trial design (such as parallel, factorial) including allocation ratio	1108
	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Not applicable
Participants	Eligibility criteria for participants	1108
	Setting and locations where the data were collected	1108
Interventions	The interventions for each group with sufficient details allow replication, including how and when they were actually administered	1108
Outcomes	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	1108
	Any changes to trial outcomes after the trial commenced, with reasons	Not applicable
Sample size	How sample size was determined	1108
	When applicable, explanation of any interim analyses and stopping guidelines	Not applicable

Randomization (method)		
Sequence generation	Method used to generate the random allocation sequence	1108
	Type of randomization; details of any restriction (such as blocking and block size)	1108
Allocation concealment mechanism	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taking to conceal the sequence until interventions were assigned	1108
Implementation	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	1108
Blinding	If done, who blinded after assignment to interventions (for example participants, care providers, those assessing outcomes- and how	1109
	If relevant, description of the similarity of interventions	Not applicable
Statistical methods	Statistical methods used to compare groups for primary and secondary outcomes	1109
	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Not applicable
Results		
Participant flow	For each group, the number of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	1109-1110
	For Each group, losses, and exclusions after randomization, together with reasons	Not applicable
Recruitment	Dates defining the periods of recruitment and follow-up	Not applicable
	Why the trial ended or stopped	Not applicable
Baseline data	A table showing baseline demographic and clinical characteristics for each group	1109
Numbers analyzed	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	1109
Outcomes and estimation	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	1110
	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable
Ancillary analyses	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Not applicable
Harms	All important harms or unintended effects in each group	Not applicable
Discussion		
Limitations	Trial limitations, addressing sources of potential bias, impressions, and, if relevant, multiplicity of analyses	1111
Generalizability	Generalizability (external validity, applicability of the trial findings	1111
Interpretation	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	1111-1113
Other information		
Registration	Registration number and name of trial registry	Not applicable
Protocol	Where the full trial protocol can be accessed, if available	Not applicable
Funding	Sources of funding and other support (such as supply of drugs), role of funders	Not applicable
Total score	Page number = 1, not mentioned = 0, irrelevant = not applicable	23/28

Author	(Jonsdottir et al., 2006)	
Topic	Checklist item	Reported on page number
Title and abstract		
	Identification as a randomized trial in the title	Not applicable
	Structured summary of trial design, methods, results and conclusions	97
Introduction		
Background and objectives	Specific background and explanation of rationale	97
	Specific objectives or hypotheses	97
Methods		
trial design	Description of trial design (such as parallel, factorial) including allocation ratio	98
	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Not applicable
Participants	Eligibility criteria for participants	98
	Setting and locations where the data were collected	Not applicable
Interventions	The interventions for each group with sufficient details allow replication, including how and when they were actually administered	98-99
Outcomes	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	98
	Any changes to trial outcomes after the trial commenced, with reasons	Not applicable
Sample size	How sample size was determined	Not applicable
	When applicable, explanation of any interim analyses and stopping guidelines	Not applicable
Randomization (method)		
Sequence generation	Method used to generate the random allocation sequence	Not applicable
	Type of randomization; details of any restriction (such as blocking and block size)	Not applicable
Allocation concealment mechanism	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taking to conceal the sequence until interventions were assigned	Not applicable
Implementation	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Not applicable
Blinding	If done, who blinded after assignment to interventions (for example participants, care providers, those assessing outcomes- and how	Not applicable
	If relevant, description of the similarity of interventions	Not applicable
Statistical methods	Statistical methods used to compare groups for primary and secondary outcomes	99
	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Not applicable
Results		
Participant flow	For each group, the number of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	99
	For Each group, losses, and exclusions after randomization, together with reasons	99
Recruitment	Dates defining the periods of recruitment and follow-up	Not applicable
	Why the trial ended or stopped	Not applicable
Baseline data	A table showing baseline demographic and clinical characteristics for each group	99

Numbers analyzed	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	99
Outcomes and estimation	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	100
	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable
Ancillary analyses	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Not applicable
Harms	All important harms or unintended effects in each group	Not applicable
Discussion		
Limitations	trial limitations, addressing sources of potential bias, impressions, and, if relevant, multiplicity of analyses	100-101
Generalizability	Generalizability (external validity, applicability of the trial findings	101
Interpretation	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	100
Other information		
Registration	Registration number and name of trial registry	97
Protocol	Where the full trial protocol can be accessed, if available	Not applicable
Funding	Sources of funding and other support (such as supply of drugs), role of funders	Not applicable
Total score	Page number = 1, not mentioned = 0, irrelevant = not applicable	17/23

Author	(Belardinelli et al., 1999)	
Topic	Checklist item	Reported on page number
Title and abstract		
	Identification as a randomized trial in the title	1173
	Structured summary of trial design, methods, results and conclusions	1173
Introduction		
Background and objectives	Specific background and explanation of rationale	1173
	Specific objectives or hypotheses	1173
Methods		
trial design	Description of trial design (such as parallel, factorial) including allocation ratio	Not applicable
	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Not applicable
Participants	Eligibility criteria for participants	1173-1174
	Setting and locations where the data were collected	Not applicable
Interventions	The interventions for each group with sufficient details allow replication, including how and when they were actually administered	1174
Outcomes	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	1174
	Any changes to trial outcomes after the trial commenced, with reasons	Not applicable
Sample size	How sample size was determined	Not applicable
	When applicable, explanation of any interim analyses and stopping guidelines	Not applicable

Randomization (method)		
Sequence generation	Method used to generate the random allocation sequence	Not applicable
	Type of randomization; details of any restriction (such as blocking and block size)	Not applicable
Allocation concealment mechanism	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taking to conceal the sequence until interventions were assigned	Not applicable
Implementation	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Not applicable
Blinding	If done, who blinded after assignment to interventions (for example participants, care providers, those assessing outcomes) and how	Not applicable
	If relevant, description of the similarity of interventions	Not applicable
Statistical methods	Statistical methods used to compare groups for primary and secondary outcomes	1175
	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Not applicable
Results		
Participant flow	For each group, the number of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	1174
	For Each group, losses, and exclusions after randomization, together with reasons	1175
Recruitment	Dates defining the periods of recruitment and follow-up	1175
	Why the trial ended or stopped	1175
Baseline data	A table showing baseline demographic and clinical characteristics for each group	1174
Numbers analyzed	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	1175
Outcomes and estimation	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	1175
	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable
Ancillary analyses	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Not applicable
Harms	All important harms or unintended effects in each group	Not applicable
Discussion		
Limitations	trial limitations, addressing sources of potential bias, impressions, and, if relevant, multiplicity of analyses	1181
Generalizability	Generalizability (external validity, applicability of the trial findings)	1181
Interpretation	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	1180-1181
Other information		
Registration	Registration number and name of trial registry	Not applicable
Protocol	Where the full trial protocol can be accessed, if available	Not applicable
Funding	Sources of funding and other support (such as supply of drugs), role of funders	Not applicable
Total score	Page number = 1, not mentioned = 0, irrelevant = not applicable	18/23

Table 8: Relevant study characteristics and results

Table 8.1: Subquestion 1: Relevant study characteristics and results

Author	Population	Outcome: peak VO_2
(Zhang et al., 2016)	Post-myocardial infarction patients LVEF 30-50% (LVEF dysfunction) Younger age: mean 58 years Male: predominant (1042/1122)	Time post-MI to initiation of ET (ET compared to control) → Significant ↑ peak VO_2 1. Acute period (6h - 7 days): MD = 1,52 (p<0.001) 2. Healing period (7-28 days): MD = 1,14 (p=0.024) 3. Healed period (> 29 days): MD = 0,62 (p=0.006)
(Gomes Neto et al., 2014)	Chronic Heart Failure Mean age: 59-67 years NYHA = II - III	Dance therapy VS non-exercise (control) ● Significant ↑ (MD = 4,86ml/kg/min) (p<0.00001) Dance therapy VS exercise ● No significant ↑ (MD = 0,15 ml/kg/min) (p=0.81)
(Ismail et al., 2013)	Chronic Heart Failure LVEF = reduced: < 40% NYHA: I - II - III - IV	<u>High intensity VS control</u> MD = 3,33 ml/kg/min (23%) (significant) (p=0.02) - Interval: MD = 3, 28 ml/kg/min (not significant) (p=0.13) - Continuous: MD = 3,94 ml/kg/min (significant) (p=0.02)
(Ismail et al., 2014)	Heart failure patients NYHA: I - II - III - IV LVEF = reduced: < 40%	<u>Intensity</u> <u>High</u>: Significant ↑ (MD: 3,3 ml/kg/min) (p=0.02) → ↑ from baseline: 23% <u>Low</u>: No significant. ↑ (p=0.57)

(Smart et al., 2012)	Heart failure patients LVEF = reduced < 50% VO2 < 24ml/kg/min NYHA I-III Mean age: 61 years	<u>Exercise group VS control group</u> - Significant ↑ 17,8% ($p<0.0001$) Changes in VO_2 peak ● Positive response: + > 5% (80% of all patients) (>0.003) ● Neutral response: +/- <5% (13% of all patients) (>0.003) ● Negative response: - >%5 (7% of all patients) (>0.003)

Table 8.2: Subquestion 2: Relevant study characteristics and results

Author	Population	Outcome: mortality, hospitalization
(Briffa et al., 2005)	Acute myocardial infarction Unstable angina 113 patients Age: 41-75 years	<u>Readmissions</u> More readmissions for the conventional group (not significant): 36 vs 29 (p=0,56)
(Dendale et al., 2005)	Post-PCI patients 223 patients → Rehabilitation: 140, 76% male, mean age 62 years → Control: 83, 65% male, mean age 68	<u>Mortality</u> Significantly lower incidence in the rehabilitation group :1 % vs 6%; (p<0,05)
(Dendale et al., 2008)	Post-PCI patients 213 patients → Rehabilitation: 113, mean age 58,6 → Control: 80, mean age 64,8	<u>Hospitalization</u> Higher in control group (not significant) (p=0,051) <u>Mortality</u> No significant difference (p≥0,05)
(Denollet & Brutsaert, 2001)	Coronary heart disease post MI and/or CABG 150 men → Rehabilitation: 78 → Standard medical care: 72 Mean age: 57,6 years	<u>Mortality</u> Significant lower mortality rate in rehabilitation: 4% vs 17%; (p=0,016)
(La Rovere et al., 2002)	Myocardial infarction: first, recent and uncomplicated	<u>Mortality</u> Lower cardiac death rate in trained patients: 12% vs 26% (not significant) (p=0,07)

	95 patients: 100% male, mean age 51 → Training: 49 → Control: 46	
(Oldridge et al., 1991)	Acute myocardial infarction 201 patients → rehabilitation: 87 → conventional care: 90 Mean age: 53	<u>Mortality</u> No significant difference (p≥0,05)
(West et al., 2012)	Acute myocardial infarction 2144 patients → Rehabilitation: 1100 → Control: 1044 Mean age: 64 years	<u>Mortality</u> No significant difference (p≥0,05) - After 1 year: RR = 1,16 - After 2 years: RR = 0,98 - After 7-9 years: RR = 0,99 <u>Hospitalization</u> No significant difference (p≥0,05)
(Zwisler et al., 2008)	Congestive heart failure Ischemic heart disease High risk of ischemic heart disease 770 patients → CCR: 380 → UC: 390 Mean age: 66	<u>Mortality</u> No significant difference (p=0,90) <u>Hospitalization</u> No significant difference (p=0,54) 55% CCR vs 56% UC

Table 8.3: Subquestion 3: Relevant study characteristics and results

Author	Population	Outcome: peak VO_2	Outcome: mortality, hospitalization
(Belardinelli et al., 1999)	Chronic heart failure patients LVEF </ 40% Mean age 59 years (+/- 14)	Exercise: sign. ↑ after 2m Exercise: no sign. ↑ after 14m (remains almost unchanged) No cardiac death: higher peak VO2 after exercise than patients who had a cardiac death	Control: sign. more hospitalizations (p=0,02) Control: significant more cardiac deaths (morality) p=0,01) Sign. higher survival rate in exercise group (p=0,01)
(Jonsdottir et al., 2006)	Chronic heart failure patients Age: <80 years	No sign. ↑ in exercise (Ex) or control (C) group No sign. difference between exercise and control group	Hospitalization: - 12m follow-up: 2 Ex, 5 C - 28m follow-up: ↑ (7 Ex, 12 C) Ex: not because of the worsening of heart failure C: 3 because of the worsening of heart failure Death (after 28m follow-up) - Ex: 2 - C: 2 During exercise: no adverse events

Table 9: Intervention characteristics

Table 9.1: Subquestion 1: intervention characteristics

Author	Intervention	Intervention mode	Intensity	Frequency	Session duration	Program duration	Follow-up period
(Zhang et al., 2016)	Exercise training VS control (usual care)	Cycling, walking, jogging (not mentioned in every study)	60-85% HRR or 70-90% peak HR or 55-85% VO_2 peak	2-5 sessions/week (1 article: every day)	20-60min	4-24 weeks	/
(Gomes Neto et al., 2014)	Dance therapy VS Control Dance therapy VS exercise	Not mentioned	Borg: 13-14 or 70% peak VO_2	3 sessions/week	40-50min	8-32 weeks	/
(Ismail et al., 2013)	Exercise training (different intensities VS control)	Not mentioned	High - 90-95% peak VO2 - 75-80% HRR - 80-90% HR peak - 15-18 Borg - 50-80% work load (steep ramp test)	High 90-426min/w (mean 166)	High 30-60min	High 8-16 weeks	/
(Ismail et al., 2014)	Exercise training (different intensities VS control)	Not mentioned	High 80% HRR 80-90% peakHR 90-95% peak VO_2	High: 3-4 sessions/w Low: 2-3 sessions/w	High: 30-45min Low: 15-30min	High: 8-12w Low: 8-22w	/

			<u>Low</u> 40% peak VO_2 50% HRmax				
(Smart et al., 2012)	Exercise training VS control	Cycling (not in one study)	50-95% peak VO_2	2-7 sessions/week	30-60min	3-9 months	/

Table 9.2: Subquestion 2: Intervention characteristics

Author	Intervention	Intervention mode	Intensity	Frequency	Session duration	Program duration	Follow-up period
(Briffa et al., 2005)	Comprehensive exercise-based outpatient cardiac rehabilitation vs Conventional care	Aerobic circuit training + resistance training + education + psychosocial counselling	/	3x/week	60-90 min	6 weeks	12 months
(Dendale et al., 2005)	Cardiac rehabilitation vs Control group	Aerobic exercise + psychological and dietary counselling Aerobic exercise = 20 min cycling + 20 min treadmill exercise + 10 min arm cycling	Close to anaerobic threshold level	3x/week	60 min	3 months	15 months
(Dendale et al., 2008)	Cardiac rehabilitation vs Control group	Aerobic exercise + psychological and dietary counselling Aerobic exercise = 20 min cycling + 20 min treadmill exercise + 10 min arm cycling	Close to anaerobic threshold level	3x/week	60 min	≥ 3 months	4,5 years
(Denollet & Brutsaert, 2001)	Multifaceted rehabilitation vs Standard medical care	Aerobic exercise + psychosocial group intervention + individual psychological therapy	Low-risk patients: 65-85% peak VO_2 High-risk patients: 50-75% peak VO_2	2-3x/week	/	3 months 36 sessions - 24 ECG-monitored	9 years

						- 12 without ECG-monitoring	
(La Rovere et al., 2002)	Exercise vs Control	Calisthenics Stationary bicycle ergometry	Determined by %HR at peak VO_2 Week 1: 75% Week 2-3: 85% Week 4: 95%	5x/week	30 min	4 weeks	10 years
(Oldridge et al., 1991)	Comprehensive rehabilitation vs Community care	Exercise + behavioral counseling Exercise: - 10 min warm-up -20-30 min treadmill walking, stationary cycle ergometry and arm ergometry - 10 min: cool-down with low-intensity activities	65% HRmax	2x/week	50 min	8 weeks	12 months
(West et al., 2012)	Comprehensive cardiac rehabilitation vs Usual care	Exercise training + health education + relaxation	/	Weekly or bi-weekly	/	6-8 weeks	7-9 years
(Zwisler et al., 2008)	Comprehensive cardiac rehabilitation vs Usual care	Exercise training + patient education + dietary counseling + smoking cessation + clinical assessment + risk factor	/	/	/	6 weeks 12 exercise sessions	

		management + psychosocial support					

Table 9.3: Subquestion 3: Intervention characteristics

Author	Intervention	Intervention mode	Intensity	Frequency	Session duration	Program duration	Follow-up period
(Belardinelli et al., 1999)	Exercise training Control group	Exercise: cycling (electronically braked cycle ergometer) - 15-20min: warm-up (stretching) - 40min: cycling - 5min: cool down Control: no exercise	60% VO_2 peak (Phase 1 and 2)	Phase 1 (8 weeks) - 3 sessions/w Phase 2 (12 month) - 2 sessions/w	60min	8 weeks: phase 1 12months: phase 2	
(Jonsdottir et al., 2006)	Training group Control group	Exercise: - 10min: warm-up (breathing exercise and arm/leg movements without resistance) - 15min: cycling - 20min: resistance training - 5min: cool down (stretching) - education: nutrition, relaxation, physical activity Control: same physical activity as before the study	Aerobic: 50% peak VO_2 (increased during program) Resistance: 20-25% 1RM (some patients increased to 35-40%)	2 sessions/w	50min	5 months	28 months (for hospitalization)

Table 10: Strengths and weaknesses of included studies

Author	Strengths	Weaknesses
(Belardinelli et al., 1999)	Assessors were blinded. Well described intervention. Randomization.	No recent article (1999). Small sample size. Most of the patients were men.
(Briffa et al., 2005)	Stratification of patients. Well described intervention.	No recent article (2005). Most of the patients were men. Small sample size.
(Dendale et al., 2005)	Adequate sample size. Well described intervention.	No recent article (2005). No randomization. Most of the patients were men.
(Dendale et al., 2008)	Long follow-up. Well described intervention.	No randomization. Most of the patients were men.
(Denollet & Brutsaert, 2001)	Comparable groups. Long follow-up. Well described intervention.	No recent article (2001) No randomization. All patients were men. Small sample size.
(Gomes Neto et al., 2014)	Recent article (2014).	One study had no adequate randomization. One two studies have been included. Number of total subjects: low. One study only included men. Search strategy is not described. Process of study selection and screening was not mentioned. Follow up unknown.
(Ismail et al., 2013)	Recent article (2013). Number of total subjects: High	Each intensity group had different number of patients (big difference) No information about gender. Follow up unknown. Few articles about high- and low-intensity.
(Ismail et al., 2014)	Recent article (2014). Number of total subjects: high	Not all the articles took gender into account. More male than female patients in the articles where they took gender into account Little data available on high intensity and low intensity. Follow up unknown.
(Jonsdottir et al., 2006)	Well described intervention. Randomization.	No recent article (2006). Most of the patients were men. Small sample size. Investigation of a not generalizable to all chronic heart failure patients.

		Not known if assessors were blinded. Only follow-up period for the assessment of hospitalizations and deaths.
(La Rovere et al., 2002)	Long follow-up Well described intervention.	No recent article (2002). All patients were men. Small sample size.
(Oldridge et al., 1991)	Stratified randomization. Well described intervention.	Old article (1991). Most of the patients were men. Not all patients were randomized.
(Smart et al., 2012)	All the included articles, except for one had the same intervention mode.	Number of total subjects: low. Most of the patients were men. Follow up unknown.
(West et al., 2012)	Recent article (2012). Blind randomization. Large sample size. Long follow-up. Well described intervention.	Most of the patients were men.
(Zhang et al., 2016)	Number of total subjects: high. Recent article (2016).	Most of the patients were men. Not known what the exact training intervention was in all the studies. Younger mean age. Follow up unknown.
(Zwisler et al., 2008)	Blinded assessment. Computer-generated central randomization. Well described intervention.	Most of the patients were men. Number of total subjects: low. Short duration of intervention.

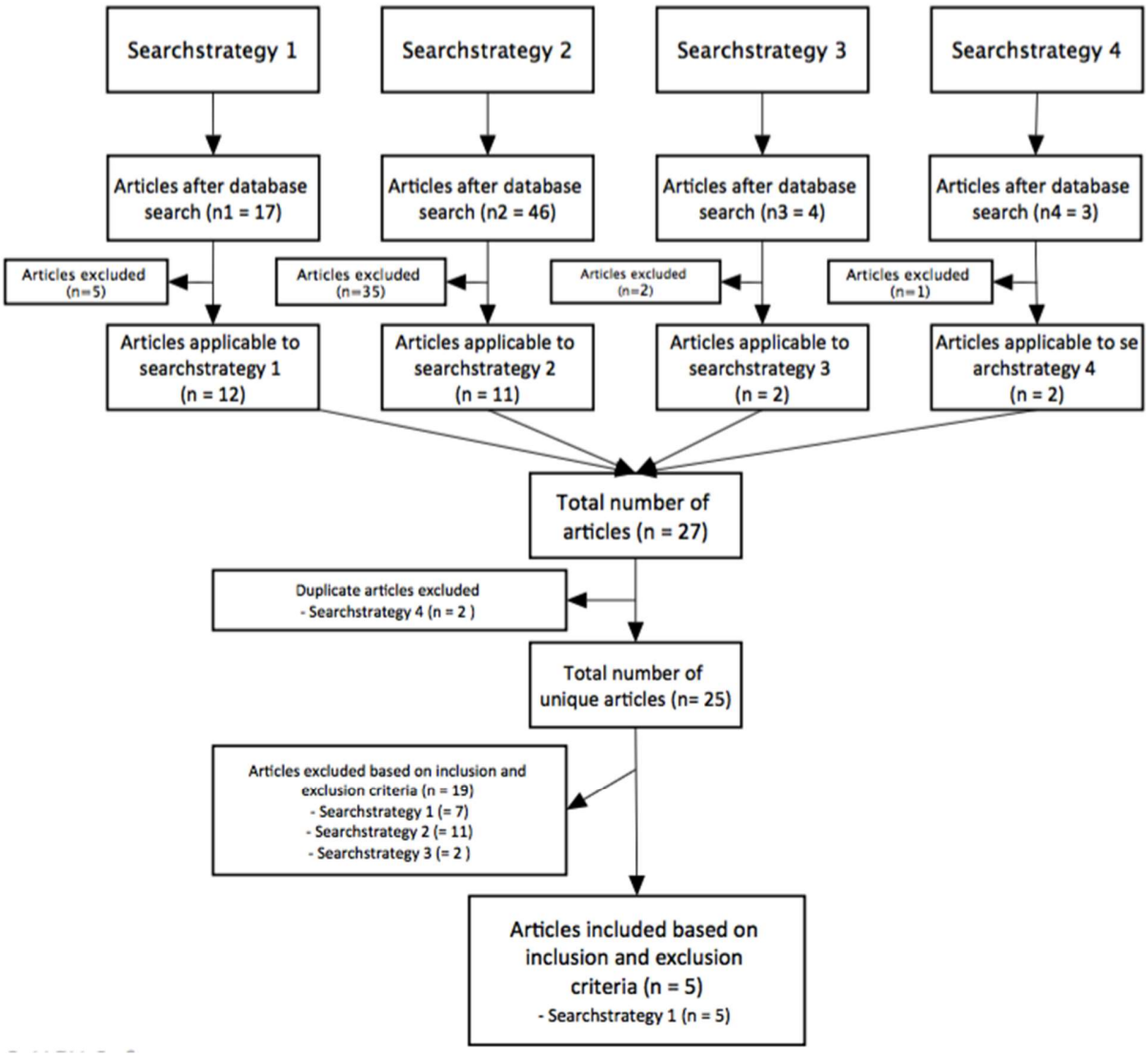

Figure 1: Flowchart study selection

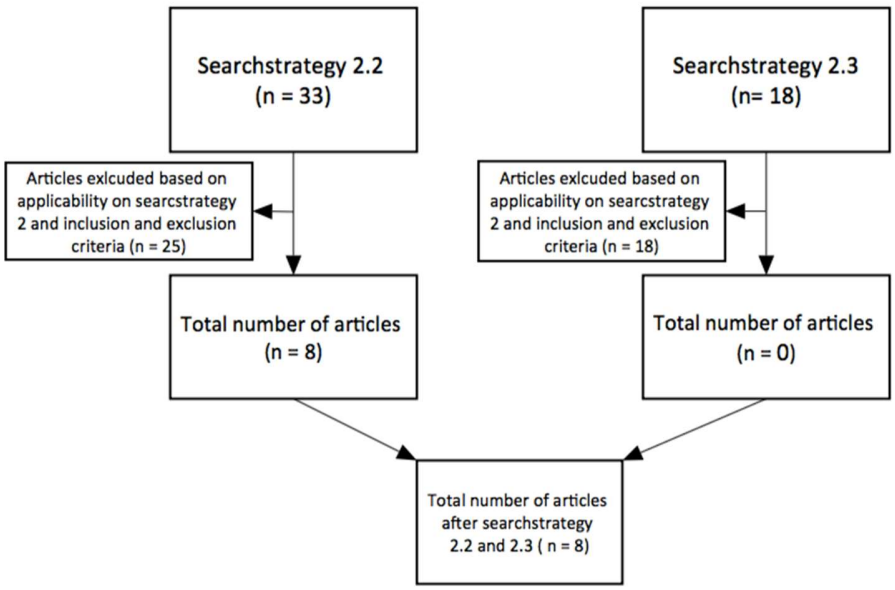

Figure 2: Flowchart extra study selection (2.2 and 2.3)

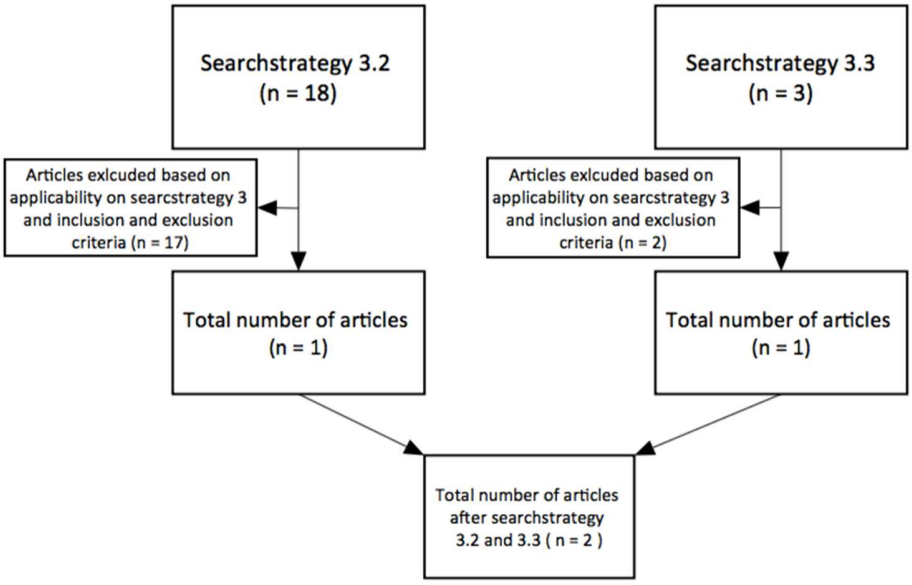

Figure 3: Flowchart extra study selection (3.2 and 3.3)

PART 2: RESEARCH PROTOCOL

1. Introduction

Cardiovascular diseases (CVD) are with its 31% the most common cause of death all over the world (www.who.int). Physical fitness is a very important prognostic factor of CVD (www.who.int) and it is related to mortality (Biswas et al., 2015; Warburton et al., 2006)

According to Pina et al. (2003), physical activity increases the aerobic capacity for which VO_2max and the anaerobic threshold (AT) are the best indicators (O'Sullivan et al., 2014).

Physical rehabilitation improves peak VO_2 and anaerobic threshold in patient with heart failure (HF) and coronary artery disease (CAD) (Nieuwland, Berkhuysen, Landsman, Lie, & Rispens, 1998; van Tol, Huijsmans, Kroon, Schothorst, & Kwakkel, 2006). It also decreases mortality and hospitalization rate in patients with HF and CAD (Clark et al., 2005; Doukky et al., 2016; O'Connor et al., 2009; Thompson, 2003; Winzer, Woitek, & Linke, 2018). But the interaction between changes in peak VO_2 or anaerobic threshold and mortality or hospitalization has barely been studied.

This research protocol fits in the domain of cardiorespiratory rehabilitation.

2. Aim of the study

We want to investigate the relationship between improvement of physical fitness and hospitalization or mortality in patients with heart failure and coronary artery disease.

2.1. Research questions

- What is the impact of physical rehabilitation on peak VO_2 and the anaerobic threshold in patients with heart failure and coronary artery disease?
- What is the impact of physical rehabilitation on mortality and hospitalization in patients with heart failure and coronary artery disease?
- What is the relationship between changes in peak VO_2 or anaerobic threshold and prognosis in patients with heart failure and coronary artery disease?

2.2. Hypotheses

- Increase in peak VO_2 and anaerobic threshold relates to a reduction of mortality and hospitalization rate in patients with heart failure and coronary artery disease.

3. Method

3.1. Research design

This study is a retrospective observational study.

3.2. Participants

The study will analyse patients with heart failure and coronary artery disease.

3.2.1. Inclusion criteria

- Patients with heart failure or coronary artery disease
- Patients may have a high cardiovascular risk profile
- Patients who followed a rehabilitation program of 12 weeks in ReGo Hasselt
- Patients had two years of follow-up
- ≥ 18 years

3.2.2. Exclusion criteria

- Patients with COPD
- Patients with neurological disease
- Patients with cancer
- No third spirometry test (post-test) was available

3.2.3. Recruitment

The patients will be recruited from the database of the Rehabilitation and Health Centre Hasselt (ReGo).

3.3. Medical ethics

The patients received an informed written consent (document 1 in appendix). An approval was obtained from The Medical Ethics Committee of Virga Jessa and ReGo on September 9, 2016.

3.4. Intervention

The patients underwent an aerobic training intervention of 12 weeks with three sessions a week.
Each session consisted of cycling or treadmill walking or a combination of these two with resistance training. Total session duration was 40-45 minutes. The intensity at which patients performed the training was determined individually. Each patient started with the amount of VO_2 corresponding with the aerobic ventilatory threshold (VT1). During the intervention the intensity increased progressively to the amount of VO_2 corresponding with the anaerobic threshold (AT). Before (pre-) and after (post-) the intervention the patients did a cardiopulmonary exercise test on the CPX Masterscreen to determine VO_2 at VT1 and AT. Respiratory Exchange Ratio (RER), heart rate (HR), expiratory volume (V_E) and workload were also noted.

After the intervention the follow-up period of minimal two years started. In this period each hospitalization (only because of a cardiac event), length of each stay and re-events (angina pectoris, acute myocardial infarction, revascularisation (PCI or CABG) and death) were noted in each patient's personal medical file.

In this master thesis all the data will be analysed. Peak VO_2 and the corresponding RER (RERpeak), HR (HRpeak) and workload (peak workload) will be collected for each patient. The AT will also be determined. These data will be compared with hospitalization rate, length of each stay and re-events of each individual patient.

3.5. Outcome measures

3.5.1. Primary outcome measures

- Peak VO_2
- Anaerobic threshold
- Hospitalization rate
- Mortality rate

3.5.2. Secondary outcome measures

- RERpeak
- HRpeak
- Workload
- Days of hospitalization (length of stay)

The CPX Masterscreen, also called Oxycon Pro, is a gas-analyzing system which analyses VO_2, VCO_2 and RER and HR. To generate accurate respiratory data, the system is valid and reliable to obtain accurate respiratory data (Carter & Jeukendrup, 2002).

During the cardiopulmonary exercise test an electrocardiography (ECG) monitors the heart rate (Hansen et al., 2011). VO_2, V_E and RER are determined breath by breath and every ten seconds an average of these outcomes is taken (Hansen et al., 2011). Before the test starts patients get seated on the cycle for three minutes and the resting data are noted (Hansen et al., 2011). Patients cycle at a frequency of 70 rpm (Hansen et al., 2011). The workload at start and the incremental workload per minute is between 10 and 40 watts, which depends on characteristics of the patient (age, gender, body length and weight) (Hansen et al., 2011). The workload rises further than the AT of the patient (Beaver, Wasserman, & Whipp, 1986). When looking at VCO_2 as a function of VO_2, the AT can be determined by the V-slope method. The AT is reached when the VO_2 and VCO_2 curves cross each other (Beaver et al., 1986). After reaching the AT, VCO_2 and V_E will rise more steeply than VO_2 (Beaver et al., 1986). The person will experience a relative hyperventilation (Hansen et al., 2011). The maximum duration of the test is 12 minutes (Hansen et al., 2011). If RER remains below 1,15 the person did not perform a maximal exercise test (Woods, Bailey, Wood, & Johnson, 2011).

3.6 Data analysis

The data analysis for each subquestion will be executed in the program JMP Pro.

To investigate the impact of physical rehabilitation on peak VO_2 and AT in patients with HF and CAD, first it need to be checked if the data are normal distributed. When the data is normal distributed and it meets homoscedasticity, a pared t-test will be used. If homoscedasticity is not met, Wilcoxon signed-rank test will be used, as well as when the data is not normal distributed. To investigate the impact of physical rehabilitation on mortality and hospitalization, only the incidence of mortality and hospitalization is important. Therefore, no statistical analysis is needed. Finally, the relationship between peak VO_2 and AT and mortality rate and hospitalization rate will be investigated with a logistic multivariate regression model. Logistic indicates if the patients had a re-event or not. Multivariate indicates on one side peak VO_2 and AT and on the other side the characteristics of the patients (age, gender, weight, body length).

4. Time planning

A flexible time planning can be used because the measurement has already been done.

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6. Appendix

Document 1: Informed 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.

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

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.

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

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.

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.

---

[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.

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.

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)

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KNOWLEDGE IN ACTION

ZELFEVALUATIERAPPORT **WETENSCHAPPELIJKE STAGE - DEEL 1**
RWK

Student: Grauwels Martijn
Promotor: Prof. Dr. Dominique Hansen
Titel masterproef: Is there a relationship between improvement of physical fitness and mortality or hospitalization in patients with heart failure and coronary artery disease?

LITERATUURSTUDIE	Gestelde deadline	Behaald op	Reflectie
De belangrijkste concepten en conceptuele kaders van het onderzoekdomein uitdiepen en verwerken	10/02	10/02	Informatie opgezocht op internet ivm CVD.
De belangrijkste informatie opzoeken als inleiding op de onderzoeksvraag van de literatuurstudie	10/02	10/02	Informatie opgezocht op internet ivm CVD.
De opzoekbare onderzoeksvraag identificeren en helder formuleren in functie van de literatuurstudie	08/01	06/01	De onderzoeksvraag werd ook in deelvragen opgedeeld.
De zoekstrategie op systematische wijze uitvoeren in relevante databanken	08/01	16/01	Omdat de zoekstrategie niet voldoende artikels had opgelerd moesten we deze nog aanpassen.
De kwaliteitsbeoordeling van de artikels diepgaand uitvoeren	26/02	26/02	Kwaliteitsbeoordeling was op tijd af. Kleine aanpassingen (bv: score) werd later nog uitgevoerd.
De data-extractie grondig uitvoeren	28/04	30/04	De extractie van de data was iets later klaar dan verwacht door enkele fouten in de analyse.
De bevindingen ïntegreren tot een synthese	04/05	04/05	Deadline behaald. Achteraf nog ingekort.

ONDERZOEKSPROTOCOL	Gestelde deadline	Behaald op	Reflectie
De onderzoeksvraag in functie van het onderzoeksprotocol identificeren	16/05	16/05	Na overleg met Prof. Dr. Hansen.
Het onderzoeksdesign bepalen en/of kritisch reflecteren over bestaande onderzoeksdesign	16/05	16/05	Na overleg met Prof. Dr. Hansen.
De methodesectie (participanten, interventie, uitkomstmaten, data-analyse) uitwerken	20/05	20/05	Na overleg met Prof. Dr. Hansen en thesis partner.

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ACADEMISCHE SCHRIJVEN	Gestelde deadline	Behaald op	Reflectie
Het abstract to the point schrijven	30/05	05/06	Abstract was tijdig geschreven, maar is achteraf beknopter herschreven.
De inleiding van de literatuurstudie logisch opbouwen	04/05	06/05	Na overleg met Prof. Dr. Hansen zijn nog enkele aanpassingen gebeurd.
De methodesectie van de literatuurstudie transparant weergegeven	26/2	26/2	Methode was goed uitgeschreven. Enkel grammaticale correcties aangebracht na afspraak met Prof. Dr. Hansen.
De resultatensectie afstemmen op de onderzoeksvragen	28/04	30/04	De resultatensectie was iets later klaar dan verwacht door enkele fouten in de analyse.
In de discussiesectie de bekomen resultaten in een wetenschappelijke tekst integreren en synthetiseren	14/05	10/05	De discussie was vroeger klaar dan verwacht. Dit door het reeds noteren van discussiepunten tijdens het schrijven van de resultaten.
Het onderzoeksprotocol deskundig technisch uitschrijven	20/05	05/06	Aanvankelijk onduidelijke verwachtingen. Na bespreking met Prof. Dr. Hansen aangepast en goedgekeurd.
Referenties correct en volledig weergeven	01/06	11/06	Volledige referentielijst in orde. Pas na de deadline gesplitst in aparte referentielijsten.

ZELFSTUREND EN WETENSCHAPPELIJK DENKEN EN HANDELEN	Aanvangsfase	Tussentijdse fase	Eindfase
Een realistische planning opmaken, deadlines stellen en opvolgen	Onvoldoende	Goed	Goed
Initiatief en verantwoordelijkheid opnemen ten aanzien van de realisatie van de wetenschappelijke stage	Voldoende	Goed	Goed
Kritisch wetenschappelijk denken	Voldoende	Goed	Zeer goed
De contacten met de promotor voorbereiden en efficiënt benutten	Goed	Zeer goed	Zeer goed
De richtlijnen van de wetenschappelijke stage autonoom opvolgen en toepassen	Voldoende	Goed	Goed
De communicatie met de medestudent helder en transparant voeren	Zeer goed	Zeer goed	Zeer goed
De communicatie met de promotor/copromotor helder en transparant voeren	Goed	Zeer goed	Goed
Andere verdiensten:	/	/	/

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ZELFEVALUATIERAPPORT **WETENSCHAPPELIJKE STAGE - DEEL 1**
RWK

Student: Janssens Wenche
Promotor: Prof. Dr. Dominique Hansen
Titel masterproef: Is there a relationship between improvement of physical fitness and mortality or hospitalization in patients with heart failure and coronary artery disease?

LITERATUURSTUDIE	Gestelde deadline	Behaald op	Reflectie
De belangrijkste concepten en conceptuele kaders van het onderzoekdomein uitdiepen en verwerken	10/02	10/02	Informatie opgezocht op internet ivm CVD.
De belangrijkste informatie opzoeken als inleiding op de onderzoeksvraag van de literatuurstudie	10/02	10/02	Informatie opgezocht op internet ivm CVD.
De opzoekbare onderzoeksvraag identificeren en helder formuleren in functie van de literatuurstudie	08/01	06/01	De onderzoeksvraag werd ook in deelvragen opgedeeld.
De zoekstrategie op systematische wijze uitvoeren in relevante databanken	08/01	16/01	Omdat de zoekstrategie niet voldoende artikels had opgelerd moesten we deze nog aanpassen.
De kwaliteitsbeoordeling van de artikels diepgaand uitvoeren	26/02	26/02	Kwaliteitsbeoordeling was op tijd af. Kleine aanpassingen (bv: score) werd later nog uitgevoerd.
De data-extractie grondig uitvoeren	28/04	30/04	De extractie van de data was iets later klaar dan verwacht door enkele fouten in de analyse.
De bevindingen ïntegreren tot een synthese	04/05	04/05	Deadline behaald. Achteraf nog ingekort.

ONDERZOEKSPROTOCOL	Gestelde deadline	Behaald op	Reflectie
De onderzoeksvraag in functie van het onderzoeksprotocol identificeren	16/05	16/05	Na overleg met Prof. Dr. Hansen.
Het onderzoeksdesign bepalen en/of kritisch reflecteren over bestaande onderzoeksdesign	16/05	16/05	Na overleg met Prof. Dr. Hansen.
De methodesectie (participanten, interventie, uitkomstmaten, data-analyse) uitwerken	20/05	20/05	Na overleg met Prof. Dr. Hansen en thesis partner.

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De inleiding van de literatuurstudie logisch opbouwen	04/05	06/05	Na overleg met Prof. Dr. Hansen zijn nog enkele aanpassingen gebeurd.
De methodesectie van de literatuurstudie transparant weergegeven	26/2	26/2	Methode was goed uitgeschreven. Enkel grammaticale correcties aangebracht na afspraak met Prof. Dr. Hansen.
De resultatensectie afstemmen op de onderzoeksvragen	28/04	30/04	De resultatensectie was iets later klaar dan verwacht door enkele fouten in de analyse.
In de discussiesectie de bekomen resultaten in een wetenschappelijke tekst integreren en synthetiseren	14/05	10/05	De discussie was vroeger klaar dan verwacht. Dit door het reeds noteren van discussiepunten tijdens het schrijven van de resultaten.
Het onderzoeksprotocol deskundig technisch uitschrijven	20/05	05/06	Aanvankelijk onduidelijke verwachtingen. Na bespreking met Prof. Dr. Hansen aangepast en goedgekeurd.
Referenties correct en volledig weergeven	01/06	11/06	Volledige referentielijst in orde. Pas na de deadline gesplitst in aparte referentielijsten.

ZELFSTUREND EN WETENSCHAPPELIJK DENKEN EN HANDELEN	Aanvangsfase	Tussentijdse fase	Eindfase
Een realistische planning opmaken, deadlines stellen en opvolgen	Onvoldoende	Goed	Goed
Initiatief en verantwoordelijkheid opnemen ten aanzien van de realisatie van de wetenschappelijke stage	Voldoende	Zeer goed	Zeer goed
Kritisch wetenschappelijk denken	Voldoende	Goed	Zeer goed
De contacten met de promotor voorbereiden en efficiënt benutten	Goed	Zeer goed	Zeer goed
De richtlijnen van de wetenschappelijke stage autonoom opvolgen en toepassen	Voldoende	Goed	Zeer goed
De communicatie met de medestudent helder en transparant voeren	Zeer goed	Zeer goed	Zeer goed
De communicatie met de promotor/copromotor helder en transparant voeren	Goed	Zeer goed	Goed
Andere verdiensten:	/	/	/

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UHASSELT
KNOWLEDGE IN ACTION

VOORTGANGSFORMULIER WETENSCHAPPELIJKE STAGE DEEL 1

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
		Promotor: Copromotor: Student(e): Student(e):
30/10	Contract ondertekenen Algemene afspraken	Promotor: Copromotor: Student(e): Student(e):
~~2/11~~		Promotor: Copromotor: Student(e): Student(e):
8/11	Bespreking zoekstrategie & onderzoeksvraag.	Promotor: Copromotor: Student(e): Student(e):
16/11	Aangepaste zoekstrategie bespreken	Promotor: Copromotor: Student(e): Student(e):
26/12	Bespreking geïncludeerde artikels & analyse quality assessment.	Promotor: Copromotor: Student(e): Student(e):
04/04	Bespreking resultatenanalyse.	Promotor: Copromotor: Student(e): Student(e):
04/05	Feedback inleiding Info protocol	Promotor: Copromotor: Student(e): Student(e):
01/06	Bespreking officiële versie	Promotor: Copromotor: Student(e): Student(e):
		Promotor: Copromotor: Student(e): Student(e):