Graduate thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences

Pernille Hagen

Achievement of current guideline levels regarding cardiovascular risk factors after cardiac rehabilitation

A randomised study

Graduate thesis in Medicine
Supervisor: Inger-Lise Aamot Aksetøy and Elisabeth Kleivhaug
Vesterbekkmo
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Abstract

Background: Studies conducted both in Norway and Europe have found low achievement of current guidelines regarding cardiovascular risk factors. Physical activity (PA) positively affects several risk factors of coronary heart disease (CHD), but few CHD patients have an adequate PA-level. Extended cardiac rehabilitation (CR) increases maintenance of PA-level.

Objectives: The purpose of the study was to explore whether extended CR had an additional effect on the lipid profile in patients with CHD. Further, we wanted to investigate the achievement of current guidelines in regards of PA.

Design: A randomised controlled study

Methods: Participants (112 men/22 women) who had completed standard CR were randomly assigned to either extended cardiac rehabilitation run by municipality (MBG), home-based extended cardiac rehabilitation (HBG) or a control group (CG). The extended cardiac rehabilitation groups (MBG and HBG) completed 1 session of interval training (4 times 4 minutes) for 8 weeks and were encouraged to two optional additional exercises per week. After 8 weeks the MBG got a follow-up session every third month until 1 year after inclusion. The control group received standard lifestyle advice at baseline and had no follow-up throughout the year. Primary outcome was measurements of change in lipids, including total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides. Secondary outcomes were change in PA, HbA1c and body mass index.

Results: At 1-year follow up 50% of all participants and 56% of participants on high-intensive statin therapy (HIST) achieved LDL-C levels below 1,8 mmol/L. 73 (88%) participants were found adherent to their lipid lowering therapy. The majority of participants (97% and 91,5%) met the recommended target for both triglycerides and weekly level of moderate PA, respectively. Total cholesterol and LDL-C levels increased significantly within HBG and CG. Triglyceride levels decreased significantly in MBG. HbA1c decreased significantly within MBG and CG. There were significant differences between groups regarding HDL-C, triglycerides and HbA1c.

Conclusion: Our findings suggest that current lipid lowering therapy in patients with CHD is inadequate. We suggest that a larger proportion of patients should be using HIST, Ezetimibe combined with statins or PCSK9 inhibitors. Further, extended cardiac rehabilitation was not found to have any additional effect on the lipid profile. The majority of participants reached recommended PA-levels at both baseline and 1-year, suggesting that extended CR does not lead to higher PA-levels.

Keywords: Cardiac rehabilitation, exercise, lipids, coronary heart disease

Selected abbreviations

ACC – American College of Cardiology

ACEI – angiotensin converting enzyme inhibitor

AHA – American Heart Association

ARB – angiotensin receptor blocker

BMI – body mass index

CG – control group

CHD – coronary heart disease

CR – cardiac rehabilitation

CVD – cardiovascular disease

DALY – disability-adjusted life years

DM – diabetes mellitus

ESC – European Society of Cardiology

GP – general practitioner

HBG – home-based group

HDL-C – high-density lipoprotein cholesterol

HIST – high-intensity statin therapy

LDL-C – low-density lipoprotein cholesterol

LIST – low-intensity statin therapy

MBG – municipality-based group

MI – myocardial infarction

MIST – moderate-intensity statin therapy

PA – physical activity

RCT – randomised controlled trial

Acknowledgements

This thesis was written during spring of 2019 as a part of the study of medicine at the Norwegian University of Science and Technology, Faculty of Medicine and Health Science. I have learned a lot about how clinical trials can be conducted through observing testing of participants and working with the collected data.

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Trondheim, 22th of May 2019
Pernille Hagen

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1.0 Introduction

1.1 Coronary heart disease – definition, morbidity and mortality

Coronary heart disease (CHD) is a subgroup of cardiovascular disease (CVD)[1,2]. CHD is mostly caused by atherosclerosis, which is an inflammatory process where fat and cholesterol are deposited inside the arterial wall and leads to the development of plaque, arterial narrowing and thus impaired flow of oxygen-rich blood to the heart. Myocardial infarction (MI) occurs when plaques loosen, cause a thrombus and cut off the blood supply and consequently causes tissue damage. Angina pectoris (chest pain) develops when the coronary arteries fail to adequately supply the heart with oxygen and thus causes ischaemia, without causing tissue damage. Ischaemia is inducible when oxygen demand in the heart increases, which could happen during physical activity or other stress[1].

CVD is the leading cause of death globally[2], accounting for 31% of all deaths in 2016, thus representing a major challenge in public health. Three out of four of these deaths occur in low- or middle-income countries. Mortality and morbidity of CVD has significantly declined in high income countries the past two decades due to better treatment and improved risk factor management [1,3], and Norway is showing a similar trend (Figure I). More than half of the reduction in mortality is due to improved risk factor profiles in the population, where cholesterol levels, blood pressure and smoking cessation has been the most important[2,3]. Improved medical therapy leads to more patients surviving acute events, and consequently more people live with established CHD[4]. One fifth of the Norwegian population live with CVD or are in great risk of developing the disease[5]. In Europe the number of people living with CVD was 85 millions in 2015[6].

Disability-adjusted life years (DALY) is a measurement of years of life lost due to early death from a disease and years lived with a disability due to a disease, where one DALY is the loss of one year of healthy life[7]. CHD was the cause of 10% of the total loss of DALY in European counties in 2015, showing that it greatly contributes to morbidity in high-income countries[6]. The burden of disease is expected to increase due to an increased incidence of obesity, metabolic syndrome and diabetes mellitus (DM), together with the increased proportion of elderly[3]. As the prevalence of people living with CHD increases, effectiveness and accessibility of health services for people with CHD is of great importance[8].

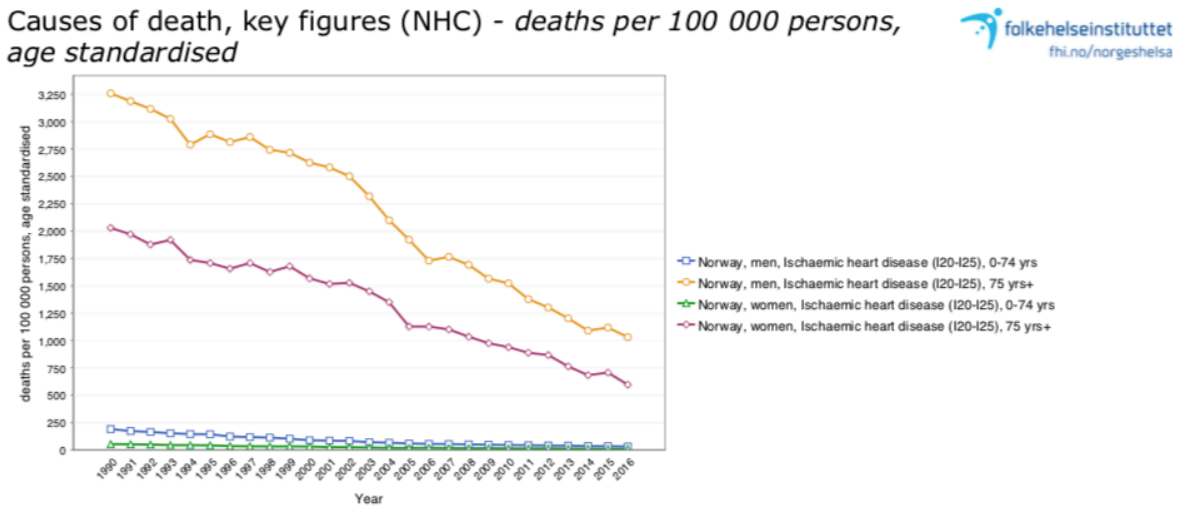

Figure I. Ischaemic heart disease as cause of death per 100 000 persons in Norway. Source: Folkehelseinstituttet[5].

1.2 CHD – risk factors

There are several risk factors for developing CVD, including a number of behavioural (smoking, physical inactivity, unhealthy diet, harmful use of alcohol) and metabolic risk factors (hypertension, DM, raised blood lipids, overweight and obesity)[1,2]. Both the behavioural and metabolic factors are highly modifiable and should be targeted to prevent CVD. In line with this, the Tromsø Study[9] found changes in coronary risk factors to account for 66% of the decline in total CHD between 1995 and 2010, where favourable changes in cholesterol, blood pressure, resting heart rate, smoking and physical activity amounted for the largest change. During the same time period, body mass index (BMI) and DM increased. A study done on the effect of physical inactivity on major non-communicable diseases worldwide[10] found physical inactivity to be a risk factor on the same level as smoking and obesity.

In addition to the behavioural and metabolic risk factors, there are several non-modifiable risk factors. This includes age, gender and genetic predisposition. Age and gender are important predictors, as men and elderly have higher incidence rates of CHD[3,11]. A large, international case-control study on patients with acute MI (the INTERHEART study)[12] confirms this as they found median age of first MI in men to be nine years lower than in women. They found several risk factors, including smoking, adverse lipid profile, hypertension and DM to be a greater relative risk in younger than in elderly individuals with acute MI. They also found raised lipids and smoking to be two of the most important risk factors for CHD worldwide.

1.3 Cholesterol and triglycerides as cardiovascular risk factors

Low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides constitute the lipoprotein profile[1]. Total blood cholesterol is made up of LDL-C, HDL-C and other lipid components. These lipids circulate in the blood plasma in relation to different proteins (apolipoproteins)[3]. LDL-C is the biggest carrier of cholesterol and it is a major risk factor for developing CVD. LDL-C particles are deposited in the arterial wall and thus lead to atherosclerosis. Reducing LDL-C significantly lowers the frequency of CVD[13]. The reduction of cholesterol in the general population is one of the major reasons for a reduced incidence of CVD the last two decades[3], confirmed by the Tromsø Study[9], which found favourable changes in cholesterol to account for 32% of the decrease in incidence of CHD.

HDL-C is considered the "good" cholesterol as it can transport cholesterol out of the arterial wall[1]. HDL-C and triglycerides have earlier been found to be highly relevant in the atherosclerotic process[14]. It has been assumed that low HDL-C concentration independently increases risk of CVD. However, the causality between HDL-C and CVD are somewhat uncertain, as raising HDL-C with drugs have not shown any reduction in cardiovascular events, but HDL-C is still found to be a strong predictor of risk for CVD[15].

Hypertriglyceridemia is considered a risk factor for CVD, but it is also here debated whether it is an independent risk factor[16]. Either way, it does not seem as important as cholesterol for developing CVD[1,17]. The treatment target remains at <1,7 mmol/L in patients in high risk for CVD, but there are no randomised controlled trials (RCT) to set treatment target for triglycerides[3].

1.4 Cardiac rehabilitation and physical activity in CHD-patients

Cardiac rehabilitation (CR) are secondary preventive programs for patients with established CHD (e.g after MI, revascularization, coronary artery bypass graft surgery), that aims to restore health, modulate risk factors and implement a long-term healthy lifestyle in patients. Exercise-based CR are highly recommended by both the European Society of Cardiology (ESC), the American Heart Association (AHA) and the American College of Cardiology (ACC) for patients with CHD [3,18]. CR should not only consist of exercise, but rather be a multifaceted and multidisciplinary intervention, which includes the core components of CR;

patient assessment, physical activity (PA) counselling, exercise training, diet counselling, weight control management, lipid management, blood pressure monitoring, smoking cessation and psychosocial management[4].

Exercise is an important part of CR as it improves risk factor profile by contributing to weight loss, glycaemic control, improved blood pressure and improved lipid profile and insulin sensitivity [1,3,19]. The ESC-guidelines states that adults should be moderately active at least 30 minutes 5 days per week (≥150 minutes every week) or spend 75 minutes in vigorous activity per week[3]. Several systematic reviews[8,20] have found exercise-based CR to reduce cardiovascular mortality, reduce hospital admissions and improve quality of life. Further, CR has been found to benefit anyone affected by CVD[4], which underlines the importance of it being offered and available to all patients. However, participation remains suboptimal, especially in women and elderly[21,22]. Integration of CR programs today is inadequate, with only about one third of CHD patients receiving it[23,24]. It is also a problem that CR surveillance are too short, and the patients are not able to fully change their risk behaviour in long-term. It is estimated that 50-80% stops exercising within one year after participating in CR[25-27]. Participants in extended CR programs has been found to have improved exercise maintenance compared to standard-length CR[28-30].

Home-based CR has been attempted the last decade to lead to an easier and more accessible way to have more patients participating[31]. Several systematic reviewes[31,32] shows that home-based CR are equally effective as centre-based CR in improving clinical and health-related quality of life in patients with CHD. They also found marginal evidence that a higher proportion of patients completed CR when it was home-based.

An exercise-based CR program typically consists of 12 weeks of 2 exercise sessions per week after discharge from hospital, in moderate or vigorous intensity. Interval training at vigorous intensity has been found to be effective in improving cardiovascular risk factors and increasing exercise capacity compared to exercise at moderate intensity[33-36]. It is well tolerated in patients with stable heart disease, and it is suited for exercise at home for motivated patients[37].

1.5 Effect of exercise and CR on lipids

Research has shown that PA improves many CVD risk factors, including decreasing LDL-C and triglyceride levels and increasing HDL-C levels[38,39]. However, these findings are somewhat inconsistent. A report from ACC/AHA on lifestyle management to reduce cardiovascular risk from 2013[40] found with a moderate strength of evidence that aerobic physical exercise in adults reduces LDL-C with 3-6 mg/dl (0,08-0,16 mmol/L) on average compared to control interventions. The same report found that aerobic physical exercise had no effect on HDL-C and triglyceride concentration.

A recent systematic review[41] looked at the effect of physical exercise on LDL-C levels in people free from CVD and without cholesterol lowering treatment. They found that aerobic exercise of both low and moderate intensity was not proven to be significantly related to LDL-C concentration. A few studies included in the review suggests that exercise has a significantly effect on LDL-C levels in patients with dyslipidaemia. Another study has compared aerobic interval exercise to continuous moderate exercise as treatment for metabolic syndrome[42]. The syndrome consists of several risk factors for CVD, including hypertension, dyslipidaemia, impaired glycaemic control and abdominal obesity. They found that exercise intensity is an important factor for improving risk factors of the metabolic syndrome.

A systematic review[32] compared blood lipids in home-based CR versus centre-based CR. Their pooled analyses found no difference between groups in total cholesterol and LDL-C levels, some evidence that HDL-C levels were higher after centre-based CR and slightly lower triglycerides after centre-based CR. An earlier systematic review[31] found in all studies but one that there was evidence of a reduction in total cholesterol, LDL-C and triglycerides, and an increase of HDL-C in both home-based CR and centre-based CR. A study comparing extended CR to standard CR[26] found a favourable effect on HDL-C and triglycerides levels in the extended group, and no difference between groups in total cholesterol and LDL-C levels. In summary, results regarding the lipid profile after extended CR is conflicting.

1.6 Lipid lowering therapy

An important part of secondary prevention of CHD and CR programs is lipid management. Current guidelines states that LDL-C levels should be lowered to <1,8 mmol/L or reduced by at least 50% if the baseline value is between 1,8 and 3,5 mmol/L in patients with established

CHD[3]. Several meta-analysis[13,43] have found that a reduction of 1,0 mmol/L in LDL-C concentration reduces the risk of major coronary events, coronary revascularization and stroke by about one fifth, irrespective of initial lipid profile and gender[44]. A systematic review[45] found that statins can lower LDL-C by an average of 1,8 mmol/L and lead to an 60% reduction of cardiac events. The studies found no evidence that lowering LDL-C concentration below 2,0 mmol/L, or even below 1,8 mmol/L, increases the risk of death from other causes, including cancer.

According to ACC/AHA guidelines on cholesterol[46], high-intensive statin therapy (HIST) is defined as a dose that lowers LDL-C on average by approximately ≥50%, moderate-intensive statin therapy (MIST) lowers LDL-C on average by approximately 30- <50% and low-intensive statin therapy (LIST) lowers LDL-C on average by approximately <30%[46]. A meta-analysis of four RCTs[47] comparing HIST to MIST found HIST to provide a significant benefit in lowering CVD events compared to MIST. One of these RCTs[48] concluded that patients who had suffered from an acute coronary syndrome benefited from an early and continued start of HIST. They also found significantly more liver-related side effects with HIST than MIST. Another RCT [49] found HIST to reduce progression of coronary atherosclerosis compared to MIST. Further, a meta-analysis[43] found HIST to lead to an 0,51 mmol/L further reduction of LDL-C compared to standard regimen.

Ezetimibe lowers cholesterol by reducing absorption of cholesterol from the intestine[50]. The IMPROVE-IT study[51] found Ezetimibe combined with statin to significantly lower the risk of MI and ischaemic stroke, and the combination of drugs reduced LDL-C levels to a median of 1,4 mmol/L, as compared to 1,8 mmol/L in the statin-monotherapy group. This represented a further LDL-C reduction of 24% when Ezetimibe was combined with statins compared to statin-monotherapy, as is similar to the reduction found in other studies[52,53]. They also found that lowering LDL-C levels below the current recommended level provided additional benefits in reducing major cardiovascular events.

Evolocumab is a type of monoclonal antibody that inhibits proprotein convertase subtilisin-kexin type 9 (PCSK9) that has emerged the last years as an efficient alternative for lowering LDL-C levels. Studies have found Evolocumab to lower LDL-C levels by up to 60% compared to placebo[54,55]. A study following patients for a median of 2,2 years who received background standard statin therapy and either Evolocumab or placebo on top found that those

receiving both statins and Evolocumab lowered their LDL-C by 59% to a median of 0,78 mmol/L and also significantly reduced the risk of CVD events, with a 20% reduction in risk of cardiovascular death, MI or stroke[55]. These findings also support that lowering LDL-C levels below 1,8mmol/L further reduces the risk of new CVD events.

Norwegian national guidelines[56] states that treatment with HIST is the first choice in patients with established CHD. Second-line treatment is Ezetimibe combined with a statin, and it should be considered as an alternative if patients are intolerant of statins or when patients does not achieve recommended level of LDL-C. Finally, treatment with PCSK9 inhibitors might be given to those with LDL-C levels ≥4 mmol/L on ongoing lipid lowering therapy.

1.7 Side effects and adherence to lipid lowering therapy

Statin therapy is generally safe and well tolerated, but side effects appear relatively frequent in clinical practice. Muscle symptoms appear to be the most common with 7-29% of patients reporting it[57]. In a survey done on 10 138 current and former statin users[58], 63% reported to have discontinued medical therapy due to side effects, with muscle symptoms being the most frequent reason. However, a systematic review done on several RCTs[59] found common side effects reported from statin use (eg. muscle symptoms, fatigue, rhabdomyolysis or rise in creatinine kinase >10 upper limit to normal) to be just as frequent in placebo-groups as in those treated with statins[59]. A meta-analysis indicated that statins led to a small increase in DM incidence[60]. The risk seems to somewhat increase with HIST compared to MIST[61].

A meta-analysis done on cardioprotective drug adherence[62] showed that approximately one third of patients with established CHD were not adherent to the drugs prescribed (including statins). Another study assessing adherence in statin-therapy[63] found a very modest reduction in adherence in HIST compared to MIST, and although it was statistically significant, they concluded that it had most likely no clinically significance. Irrespective of the dose of statin used, almost one-quarter of the patients were found to be non-adherent. Both of these studies differ from the latest EUROASPIRE study[24] where 81% reported to be fully adherent to lipid-lowering drugs. A study comparing HIST to MIST[64] found a rate of discontinuation in medication due to adverse events to be 7,2% and 5,2%, respectively. In the IMPROVE-IT study, the rate of discontinuation in medication due to adverse events was reported to be 10,6% in Ezetimibe combined with statins as opposed to 10,1% in statin monotherapy[51].

1.8 Implementation of ESC-guidelines and risk factor control in CHD-patients

The EUROASPIRE studies[23,24,65] have investigated the implementation of the ESC-guidelines in clinical practice all over Europe for more than two decades, starting in 1995. They have discovered that risk factor control is poor, even though a large proportion of participants reports using cardio preventive drug therapy. Only about one third of all CHD patients participate in a CR program. The EUROASPIRE V, carried out between 2016 to 2018, supports the findings of the earlier surveys, as they found 38% of participants to be obese (BMI ≥ 30kg/m^2), 66% had inadequate PA level, 42% had hypertension (blood pressure ≥ 140/90 mmHg) and 71% had LDL-C levels ≥1,8 mmol/L. 93% used anti-platelets, 81% beta-blockers, 75% angiotensin converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) and 80% used statins. The studies have found an increasing proportion of patients taking lipid lowering drugs, but patients still struggle to meet recommendations of LDL-C.

These findings are supported by the NOR-COR survey[66], done in two hospitals in Norway between 2011 and 2014, including 1127 patients. They found obesity in 34% of the patients and 60% were physically inactive. 46% were hypertensive and 57% had LDL-C ≥ 1,8 mmol/L, even though 93% were taking blood-pressure lowering agents and statins. The CLARIFY study, a 5-year observational longitudinal cohort-study[67] had similar findings. 78% of the participants were overweight and 30% were obese, 35% had hypertension. Lipid-lowering drugs were widely used (>88%), but only 59% of patients with dyslipidaemia reached recommended target for LDL-C.

All of the abovementioned studies show that risk factor control is in general poor in patients with established CHD, and that further efforts must be made to meet recommendations.

1.9 The purpose of the study

The aim of this study was to investigate the lipid profile in participants that had completed extended CR. More specifically we wanted to assess if participants met recommendations for LDL-C levels, triglyceride levels and PA, and if any of the interventions appeared superior to others in reaching the targets. In addition, we wanted to investigate the effect and adherence of lipid lowering therapy, and achievement of LDL-C treatment target within the different groups of statins.

We hypothesized that a great proportion had achieved treatment target level of LDL-C, due to a high-prescription rate of statins and good adherence. Further, we expected the participants to be more physically active in both intervention groups compared to the controls.

2.0 Method

2.1 Study design

The current study is a subproject of the study "How to increase physical activity in patients with established heart disease". It is an RCT conducted at St. Olav's University Hospital in Trondheim, and it aims to look at the effect of two different extended CR programs compared to a control group in patients with heart disease.

The participants were randomised and stratified to either extended CR run by the municipality, a home-based extended CR program or a control group. The main RCT was approved by the Regional Committee for Medical and Health Research Ethics South East Norway (2014/92). Informed, written consent was obtained from each participant before entering the study.

2.2 Participants

During spring 2014 to spring 2017 161 eligible participants were included in the main study. Out of these, 134 participants were diagnosed with CHD and completed the 1-year follow-up tests (Figure II). Inclusion criteria were 1) men and women that due to CHD (MI, stable angina, coronary artery bypass surgery) had completed standard-length CR, 2) are clinically stable, 3) >18 years old, 4) they master the Norwegian language and 5) are able to perform maximal tread mill test. Exclusion criteria were participants with 1) unstable angina, 2) serious arrhythmias, 3) serious cardiac valve leakages, 4) heart failure or 5) a medical condition where high intensity physical exercise is contra indicated. In addition, 6) participating in another exercise study, 7) pregnancy, 8) drug abuse or 9) cognitive failure lead to exclusion.

2.3 Exercise intervention

The exercise consisted of 10-15 minutes warming up, followed by four intervals lasting 4 minutes each of running or walking at an intensity of 85-95% of peak heart rate (controlled by pulse watch, corresponds to approximately 17 on Borg scale[68]), separated by active pauses on 3 minutes, with approximately 70% of maximal heart rate to eliminate lactic acid.

1. Municipality-based group (MBG): Extended rehabilitation was under the auspices of physiotherapists, with 1 follow-up session per week for 8 weeks. They had interval training as explained above. They were in addition encouraged to do an optional

exercise two times per week on their own. After 8 weeks there was a gathering every third month with advice on exercise and diets. Total time of follow-up was 12 months.

2. Home-based group (HBG): The home-based group exercised at home on their own after being taught how to do the 4x4 minutes exercise (as explained above) and after having learned how to use a heart rate monitor watch. They were given information about diet and smoking cessation before start of intervention. They were encouraged to do at least one interval exercise per week, and in addition two optional exercises per week.
3. Control group (CG): They received no other follow-up beyond guidance and advice about exercise and physical activity, diet and smoking cessation that was given at ended rehabilitation (standard treatment), together with examinations and tests on the occasion of data collection.

2.4 Data collection

Background information such as gender, age, marital status, working conditions, progress of disease and medication were collected at start (baseline) and after ended intervention (1 year). It took place at St. Olav's Hospital and Levanger Hospital.

1. Height was measured at baseline and weight was measured in light clothes without shoes at baseline and at 1-year follow up. Overweight was defined as a BMI ≥ 25 kg/m^2 and obesity as a BMI ≥ 30 kg/m^2.
2. Waist circumference was measured using a measuring tape. Central obesity was defined as a waist circumference >88cm for women and >102 cm for men, as done in similar studies[65].
3. Fasting venous blood was drawn once at baseline and once at 1-year follow up to decide lipid profile and HbA1c. They were analysed by standard methods at the St. Olav's Hospital in Trondheim.
4. PA level was measured with the 3-axis accelerometer SenseWear Armband Pro, which is found to be accurate in measuring daily energy expenditure[69,70]. Age, gender, height and weight are taken into account. The armband was worn on the upper left arm (on the m. triceps), except when showering. All participants used the armband monitoring for a week when enrolled in the study and at 1-year follow-up. Intensity of activity was measured in metabolic equivalents of tasks (METs), which is a unit used to describe the oxygen uptake in multiples of resting oxygen requirements[71]. METs 3-6

are considered as moderate PA, which is the intensity used in this study. Data from the recorded period were analysed with SenseWear Professional 6.1.

5. Information on medical therapy was found in discharge paper after index event and in hospital records. The statin therapy were subdivided as followed[46];
   LIST: Simvastatin 10mg, Pravastatin 10-20mg, Lovastatin 20mg, Fluvastatin 20-40mg or Pitavastatin 1mg. MIST: Atorvastatin 10-20mg, Rosuvastatin 5-10mg, Simvastatin 20-40mg, Pravastatin 40-80mg, Lovastatin 40-80mg, Fluvastatin 40-80mg or Pitavastatin 2-4mg. HIST: Atorvastatin 40-80mg or Rosuvastatin 20-40mg.
6. Adherence was assessed by looking at the proportion of days covered by the prescribed drug. Information about frequency of withdrawals of drugs from pharmacies were found in the participants medical journals and were assessed together with the dosage prescribed and the size of package they withdrew to decide the proportion of days covered by the drug. Participants were considered adherent if they had taken their medication as prescribed ≥80% of the days between baseline and 1-year follow-up, which is found to be an optimal cut-off for evaluating adherence[72,73], and that are used in similar studies[63]. Data on adherence were only available in 83 out of 134 participants due to the time it took to implement the electronic prescription solution that was introduced in Norway in 2013, which means that for many participants there are no records of prescription and withdrawal available until 2015. This have affected the data available on the first participants included in our study.

2.5 Outcome measures

The primary outcome measures were mean levels of lipids, including total cholesterol, LDL-C, HDL-C and triglycerides, and change of the beforementioned between baseline and 1-year follow-up. The secondary outcome measures were change in PA, HbA1c and BMI. In addition, we investigated the proportion of participants reaching recommended levels of LDL-C, PA and triglycerides. Further, we looked at the distribution and change in cardioprotective therapy and adherence of lipid lowering therapy. All tests were performed at baseline and at 1-year follow up. The test personnel were not blinded for allocation.

2.6 Sample size

Sample size power calculations were done by the main RCT. It was based on data from earlier interventions considering mean values and variance[37,74], and it was based on calculations of maximal oxygen uptake (VO_{2max}). A difference in VO_{2max} of 1 MET is a clinically significant

change[75]. To achieve a strength of 0,9 with a significance level of 0,05, with estimated VO_{2max} at 32 ml/kg/min, a difference of 3,5 ml/kg/min (standard deviation 6) and a correlation of 0,55 between pre- and posttest, one would need to include 44 participants in each group (analysed with ANCOVA)(Stata/IC 12.1). With an estimated drop-out of 15-20% during the whole follow-up time, the aim was to include 55 participants in each group.

2.7 Randomisation

The randomisation procedure was performed after baseline tests by the unit for Applied Clinical Research at DMF, NTNU, using a web-based randomisation system.
The allocation ratio was 1:1:1 and randomisation was stratified by age and gender.
Participants were randomly allocated to either extended rehabilitation run by the municipality, a home-based CR program or a control group.

2.8 Statistical analyses

Statistical analyses were performed with IBM SPSS Statistics 25. Blood samples were not normally distributed and had outliers, but we chose to run parametric tests due to the relatively large sample size and because the tests are considered strong enough to handle the outliers. Missing data were handled by analysing the pattern, which was arbitrary, and Little's MCAR test was performed, which was not statistically significant (p= 0,490). The data were therefore considered to be missing at random. Multiple imputation was applied.

One-way between groups analysis of variance (ANOVA) and post-hoc tests were conducted to explore significant differences between groups at baseline. Within-group differences were tested with a paired sample T-test. Comparisons between groups (MBG versus HBG versus CG) were performed using a general linear model, analysis of covariance (ANCOVA), with values after intervention as the dependent variable with intervention as a factor and adjusting for baseline values. Post-hoc tests were used to investigate between which groups there were significant differences. Independent samples T-test was used to explore differences in means between gender. Pearsons correlations was used to determine associations between PA and lipid levels. Results are presented as mean ± standard deviation unless stated otherwise. In all tests, a p-value <0.05 was considered to be statistically significant.

3.0 Results

3.1 Participants and recruitment

Of 161 participants included in the original study, 134 had CHD and were still participating at the 1-year follow-up tests. The drop-out rate was 7,4%.

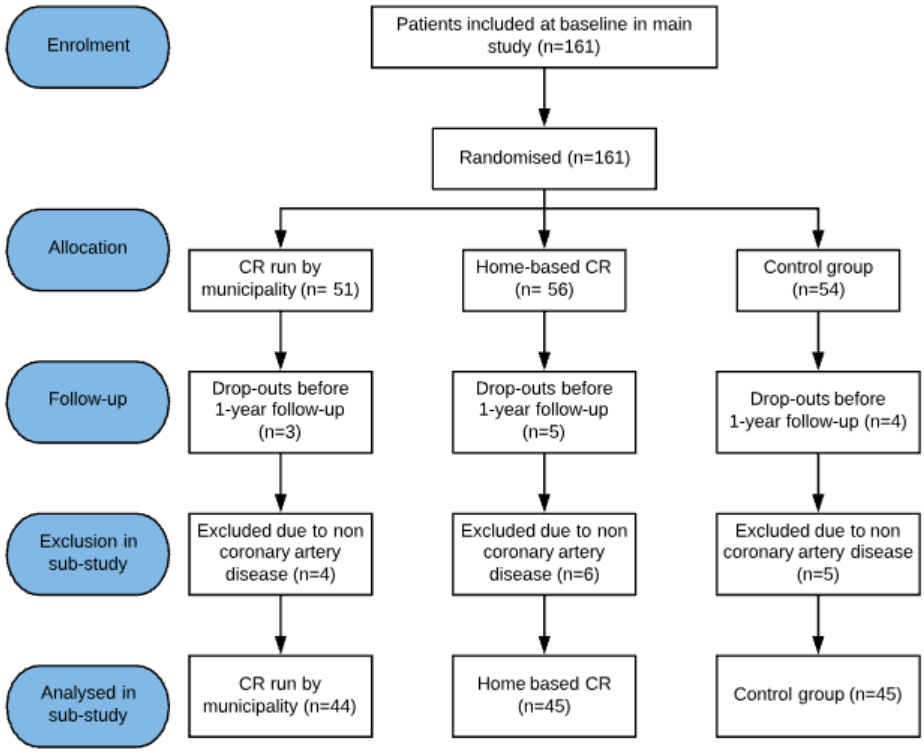

Figure II. Flow-chart illustrating enrolment, randomisation and allocation of participants through the study.

3.2 Descriptive characteristics at baseline

Baseline characteristics of the participants are presented in Table I. The groups were well matched at baseline, except from a significant difference between gender in HBG vs CG (female 11,1% vs 22,2%, p=0,001), as between waist circumference in MBG vs CG (101,41 ± 10,26 vs 98,93 ± 9,59, p=0,06). As for cholesterol lowering medication (table IV), there was a significant difference between intervention groups at baseline in regards of HIST in MBG vs CG (p= 0,029), for MIST in MBG vs HBG (p= 0,017), for LIST in MBG vs CG (p= 0,008), for no statin therapy in HBG vs CG (p= 0,001) and for other cholesterol lowering treatment in MBG vs CG (p= 0,001). For ACEI/ARB there was a significant difference at baseline between MBG vs CG (47,7% vs 33,3%, p= 0,002) and for diuretics in MGB vs HBG (2,3% vs 17,8%, p= 0,000) and in HBG vs CG (17,8% vs 4,4%, p= 0,000).

Table I. Baseline characteristics of the participants (n=134).

Mean age at baseline (Standard Deviation)	60,9 ± 8,7
Women n(%)	22(16,4)
Diagnosis	
- ST-elevation and non-ST elevation MI n(%)	70(52,2)
- Angina n(%)	28(20,9)
- Coronary artery bypass surgery n(%)	36(26,9)
Smoking	
- Previously smoked n(%)	11(8,2)
- Currently smoking n(%)	3(2,2)
BMI	
- Overweight, BMI 25-30 n(%)	64(47,8)
- Obese, BMI >30 n(%)	3(14,9)
Central obesity	
- waist circumference ≥ 88cm in women n(%)	18(81,8)
- waist circumference ≥ 102cm in men n(%)	49(43,8)
Hypertension n(%)	26(19,4)
Diabetes mellitus type II n(%)	5(3,7)
Regular PA	
≥ 150 minutes of moderate PA per week n(%)	124(92,5)
Medication at discharge after the index event	
- Single antiplatelet therapy n(%)	36(26,9)
- Double antiplatelet therapy n(%)	97(72,4)
- High-intensity statin therapy n(%)	109(81,3)
- Moderate intensity statin therapy n(%)	21(15,7)
- Low intensity statin therapy n(%)	1(0,7)
- No statin therapy n(%)	4(3,0)
- Ezetimibe n(%)	8(6,0)
- Other cholesterol lowering drugs n(%)	3(2,2)
- Beta-blockers n(%)	90(67,2)
- ACEI/ARB n(%)	54(40,3)
- Diuretics n(%)	11(8,2)
- Other blood pressure lowering drugs n(%)	11(8,2)

MI; myocardial infarction, BMI; body mass index (kg/m^2), PA; physical activity, ACEI; angiotensin converting enzyme inhibitor, ARB; angiotensin receptor blocker. Data are presented as mean ± standard deviation or as percentages.

3.3 The effect of intervention on lipid profile, glycaemic control and BMI

Intervention groups were well matched at baseline in regards of total cholesterol, LDL-C level and HbA1c-level (Table II). There was a significant difference at baseline in regards of HDL-C level between MBG and HBG (p=0,035) and between HBG and CG (p=0,006), for triglyceride levels between MBG and CG (p=0,024) and between HBG and CG (p=0,026).

3.4 Treatment target achievements in general and between gender

The proportion of all participants meeting recommendations for LDL-C at <1,8 mmol/L were 47,0% at baseline and 50% after 1 year (Figure III). 54,5% of the women reached LDL-C treatment target at both baseline and after 1 year, while the proportion for men was 45,5% at baseline and 49,1% after 1 year. Mean LDL-C level for all participants increased from 1,97 mmol/L ± 0,61 at baseline to 2,02 mmol/L ± 0,66 after 1 year (p=0,005). The means were 1,81 mmol/L ± 0,52 for women and 2,00 mmol/L ± 0,62 for men (p=0,002) at baseline. After 1 year the means were 1,85 mmol/L ± 0,46 for women and 2,05 mmol/L ± 0,69 for men (p=0,001). There was 1 participant (0,7%) with LDL-C ≥4 mmol/L at both baseline and after 1 year.

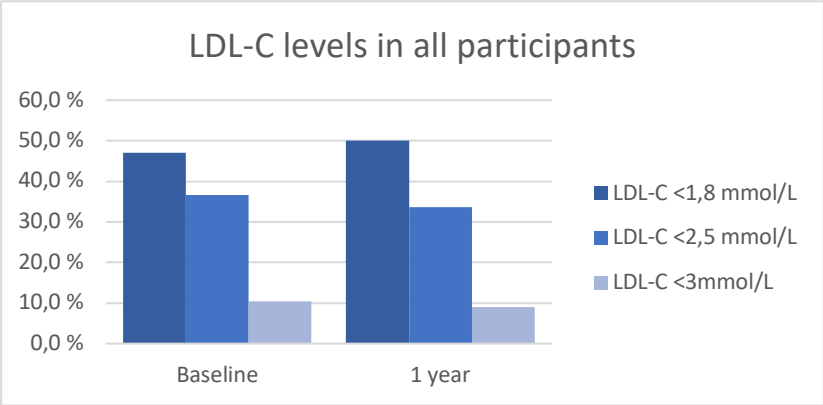

Figure III. Distribution of LDL-C levels (split into <1,8 mmol/L, 1,8-2,5 mmol/L and 2,5-3,0 mmol/L) between baseline and 1-year follow up for all participants (n=134). Data are presented as percentages.

Mean total cholesterol level for all participants had increased from 3,65 mmol/L ± 0,72 at baseline to 3,74 mmol/L ± 0,79 at 1-year (p= 0,000). HDL-C levels decreased from 1,37 mmol/L ± 0,37 at baseline to 1,35 mmol/L ± 0,39 at 1-year (p= 0,005).

Table II. Outcome measures of lipids, HbA1c and body mass index at baseline and 1-year follow-up according to intervention groups.

	MBG (n=44)			HBG (n=45)			CG (n=45)			
	Baseline	1 year	Paired samples T-test	Baseline	1 year	Paired samples T-test	Baseline	1 year	Paired samples T-test	ANCOVA
TC	3,62 ± 0,63	3,65 ± 0,73	0,449	3,64 ± 0,70	3,74 ± 0,74	0,001	3,70 ± 0,79	3,82 ± 0,89	0,003	0,058
LDL-C	1,93 ± 0,55	1,94 ± 0,57	0,676	1,99 ± 0,55	2,06 ± 0,60	0,008	1,98 ± 0,70	2,05 ± 0,79	0,033	0,114
HDL-C	1,39 ± 0,37	1,36 ± 0,41	0,026	1,31 ± 0,29	1,28 ± 0,28	0,023	1,41 ± 0,43	1,41 ± 0,45	0,970	0,040
TG	1,09 ± 0,63	0,99 ± 0,48	0,000	1,09 ± 0,45	1,09 ± 0,47	0,823	0,98 ± 0,36	0,97 ± 0,36	0,814	0,001
HbA1c	5,61 ± 0,50	5,54 ± 0,64	0,002	5,72 ± 0,78	5,72 ± 0,72	0,975	5,62 ± 0,58	5,57 ± 0,52	0,024	0,013
BMI	27,10 ± 4,26	27,33 ± 4,46	0,089	26,77 ± 3,93	27,29 ± 4,37	0,000	26,03 ± 3,11	26,39 ± 3,41	0,029	0,281

MBG; municipality-based group, HBG; home-based group, CG; control group, ANCOVA; analysis of covariance, TC; total cholesterol (mmol/L), LDL-C; low density lipoprotein cholesterol (mmol/L), HDL-C; high density lipoprotein cholesterol (mmol/L), TG; triglycerides (mmol/L), BMI; body mass index (kg/m^2). Data are presented as mean ± standard deviation.

The proportion of all participants having triglyceride levels <1,7 mmol/L were 92,3% at baseline and 92,5% after 1 year. 95,5% of the women achieved target level at both baseline and after 1 year, as for the men the proportion were 91,8% at baseline and 92,0% after 1 year. Mean triglyceride level for all participants decreased from 1,05 mmol/L ± 0,50 at baseline to 1,02 mmol/L ± 0,44 after 1 year (p=0,017). At baseline, the means were 0,96 mmol/L ± 0,29 for women and 1,06 mmol/L ± 0,53 for men (p=0,018). After 1 year the means were 0,97 mmol/L ± 0,33 for women and 1,03 mmol/L ± 0,46 for men (p=0,138).

At baseline, 90,7% had HbA1c <6%, 3,6% had HbA1c levels between 6,0- 6,5% and finally, 4,7% had levels above 6,5%. Levels ≥6,5% indicates DM according to guidelines[76]. At 1-year follow-up 88,3% had HbA1c <6%, 5,3% had HbA1c levels between 6,0-6,5% and 6,0% had levels above 6,5%. The overall means were 5,60 ± 0,55 at baseline and 5,59 ± 0,2 at 1-year (p=0,670).

The recommendations for PA are at least 150 minutes of moderate PA per week. At baseline 92,5% of all participants, 72,7% of the women, and 96,7% of the men met these recommendations. At 1-year follow-up 91,5% of all participants met the recommendations, and for women and men the proportion was 79,5% and 93,9%, respectively. On average, women were physically active for 351 minutes ± 251 per week and men for 681 ± 411 per week (p= 0,000) at baseline. After 1 year, women spent 362 minutes ± 275 and men 617 ± 377 minutes (p=0,000) in moderate PA per week.

At 1-year follow-up, there was found no association between those reaching target for LDL-C levels and those reaching PA-target (p=0,202), or between those reaching treatment target for triglycerides and those reaching PA-target (p=0,470).

Table III. Minutes of moderate PA according to intervention group and distribution of PA.

	MBG (n= 44)		Paired samples T-test	HBG (n= 45)		Paired samples T-test	CG (n= 45)		Paired samples T-test	ANCOVA
	BL	1 year		BL	1 year		BL	1 year		
MPA in MPW	614 ± 404	533 ± 293	0,001	656 ± 412	549 ± 369	0,000	618 ± 411	641 ± 435	0,306	0,000
Distribution of MPA level										
<150 MPW	9,1	8,7		5,2	7,8		6,7	4,8		
150-300 MPW	7,6	6,1		6,7	14,4		13,3	18,1		
>300 MPW	83	83		87,8	76,7		80	76,3		

MBG; Municipality based group, HBG: home-based group, CG; control group, BL; baseline, ANCOVA; Analysis of covariance, MPA; moderate physical activity (MET 3-6), MPW; minutes per week. Data are presented as mean ± standard deviation or as percentages.

3.5 Effect of lipid lowering therapy on LDL-C

Table IV. Lipid lowering therapy according to intervention groups.

	MBG (n= 44)		Paired samples T-test	HBG (n= 45)		Paired samples T-test	CG (n= 45)		Paired samples T-test	ANCOVA
	BL	1 year		BL	1 year		BL	1 year		
HIST	86,4	89,4	0,028	80,0	74,1	0,000	77,8	65,2	0,000	0,000
MIST	11,4	8,0	0,028	20,0	24,8	0,000	15,6	23,7	0,000	0,000
LIST	0	1,1	0,318	0	1,1	-	2,2	3,0	0,318	0,598
NST	2,3	2,7	0,158	0	0,7	0,318	6,7	9,3	0,001	0,000
EZT	6,8	10,6	0,049	4,4	10,4	0,000	6,7	21,5	0,000	0,000
OCH	0	0,4	0,318	2,2	1,5	0,318	4,4	3,0	0,514	0,187

MBG; Municipality based group, HBG: home-based group, CG; control group, BL; baseline, ANCOVA; Analysis of covariance, HIST; high-intensity statin therapy, MIST; moderate intensity statin therapy, LIST; low intensity statin therapy, NST; no statin therapy, EZT; Ezetimibe, OCH; other cholesterol lowering drugs. Data are presented as percentages.

After 1 year there was an overall reduction in participants using HIST (81,3% vs 76,7%), a small increase in participants using MIST (15,7% vs 18,8%) and an increase in participants on Ezetimibe (6% vs 13,8%). Participants who were not using statin therapy had changed

slightly (3,0% vs 4,4%), the same for LIST (0,7% vs 1,0%) and other cholesterol lowering drugs (2,2% vs 1,7%). The use of beta-blockers and ACEI/ARB had decreased (67,2% vs 44,5%, 40,3% vs 35,2%, respectively). Data on adherence were only available in 83 participants. 73 (88%) were considered adherent to lipid lowering therapy, 10 (12%) were non-adherent.

At 1-year follow up, the mean LDL-C level was 1,89 mmol/L ± 0,51 for participants using HIST (n=91), 2,23 mmol/L ± 0,58 for participants using MIST (n= 19) and 1,99 mmol/L ± 0,68 (n=15) for participants using Ezetimibe in combination with a statin (n=15). At baseline, 51,9% of participants using HIST (n=106), 27,8% of those using MIST (=18) and 28,6% of those using Ezetimibe in combination with statin (n=7) had reached LDL-C target of <1,8% mmol/L. The rates at 1-year follow up were 56,0%, 35,7% and 46,7%, respectively (Figure IV).

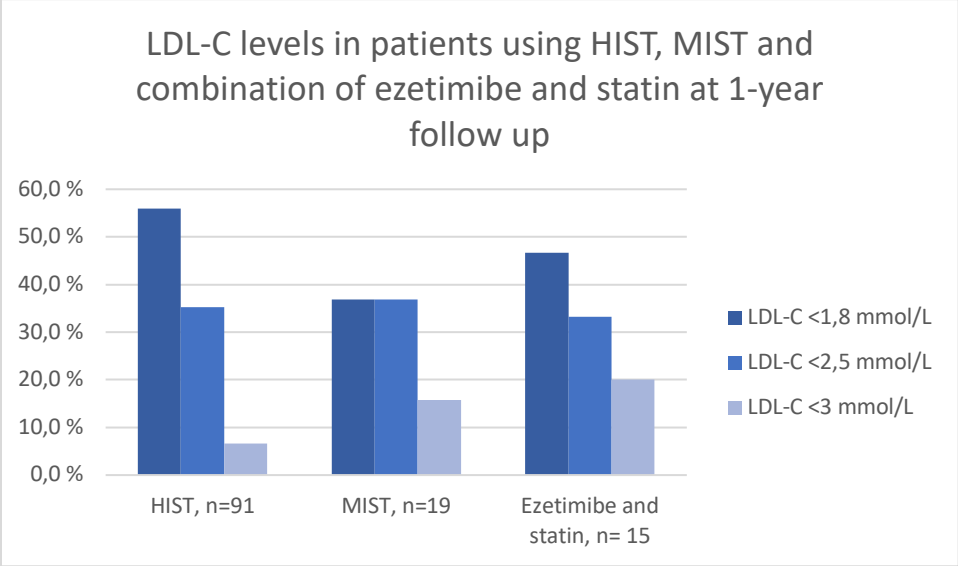

Figure IV. Distribution of LDL-C levels (split into <1,8 mmol/L, 1,8-2,5 mmol/L and 2,5-3,0 mmol/L) at 1-year follow up according to cholesterol lowering therapy. Includes only participants on HIST, MIST and those using the combination of Ezetimibe and statin (n=125). Data are presented as percentages.

4.0 Discussion

The aim of this study was to investigate the lipid profile in participants that had completed extended CR. More specifically we wanted to assess if participants met recommendations for LDL-C levels, triglyceride levels and PA, and if any of the interventions appeared superior to others in reaching the targets. We also investigated the use of cholesterol lowering therapy and looked at the effects the drug therapy had on LDL-C levels. Our hypothesis was that a large number of participants would reach LDL-C target due to lipid lowering therapy and good adherence. Further, we expected participants in MBG and HBG to be more active than in CG, and that the reduction of triglycerides would be largest in the intervention groups.

4.1 Achievement of recommended levels of LDL-C and the use of lipid lowering therapy

The main results in our study was that overall only half of the participants achieved guideline LDL-C level of less than 1,8 mmol/L at 1-year follow up. The prescription rate of statins was high at discharge, especially for HIST. The proportion of participants using HIST who reached treatment target of LDL-C was modest at 1-year follow-up. Although half the participants did not meet the recommendations, the proportion of participants prescribed with HIST decreased from baseline to 1-year follow-up. Mean LDL-C level for participants on HIST was lower than for participants on both MIST and the combination of Ezetimibe and statin at 1-year follow-up. Few participants on MIST and combination therapy reached recommended level.

Studies with similar inclusion criteria and age distribution are conducted in both Norway (NOR-COR)[66] and Europe (EUROASPIRE)[23,24,65]. The study conducted in Norway had quite similar LDL-C outcomes as our study, as they found the proportion with elevated LDL-C level to be 57%. In comparison, the latest EUROASPIRE study[24] found 71% of participants to have increased LDL-C levels.

Adherence is an important aspect here, as non-adherence could explain the low level of achievement. We found most participants to be fully adherent to their lipid lowering therapy after 1-year. Although we did not have data on all participants, one could assume that it represents a trend, and that in general, these participants are quite adherent to their drugs. The latest EUROASPIRE study[24] supports these findings, as 81% of their participants reported 100% compliance to prescribed lipid-lowering drugs.

Prescription rate of cardioprotective drugs were reported at baseline in the NOR-COR study and in EUROASPIRE V. In comparison, the prescription rate of statins was quite similar in our study and the NOR-COR study, as they found 96% to use statins. The use of beta-blockers, ACEI/ARB and diuretics was much higher in the NOR-COR study (85%, 56% and 22%, respectively). EUROASPIRE V reported 84% using lipid-lowering drugs, where only 50% used HIST. This might explain the large gap between those reaching treatment target for LDL-C in our study compared to EUROASPIRE V (29%).

As mentioned above, we found the proportion of participants using HIST to decrease from baseline to 1-year follow-up. We know that side effects appear relatively frequent in clinical practice in participants using statins (7-29% report muscle symptoms[57]), where muscle symptoms has been reported to be the most frequent reason to discontinue medication[58], and HIST has been found to have more liver side effects[48] than MIST. This might explain the reduction of participants on HIST. However, other studies have shown that difference in adherence between the two groups probably is so little that it has no clinical value[63,64]. These findings strengthen the assumption that more patients should be using HIST.

The Norwegian guidelines on secondary prevention in CVD[56] states that Ezetimibe should be considered in combination with statins as second-line treatment if guideline levels of LDL-C is not achieved. Our findings suggest that for many participants HIST alone is not sufficient to reach recommended level of LDL-C, thus the proportion of participants using the combination therapy should be much higher. The percentage of participants using Ezetimibe in combination with statin therapy in our study was modest at 1-year follow-up. These participants were found to have higher mean LDL-C than those on HIST and an overall low achievement of recommended guideline level. This might indicate that they initially had higher levels of LDL-C than other participants, and that they therefore were prescribed with the combination therapy. In other words, this does not mean that the combination of drugs is less effective than HIST. Studies also supports this, as Ezetimibe has been found to be very efficient in lowering LDL-C levels[51-53]. Another reason for these findings might be that they have lower adherence of drugs. However, there is found little difference between discontinuation of patients using Ezetimibe combined with statins compared to statins alone[51]. Further, guidelines also state that therapy with PCSK9 inhibitors could be granted if LDL-C levels are above 4 mmol/L. Our findings suggest that this applies for few of the CHD patients, but even so, it must be taken into consideration, as these patients will be in higher risk of

cardiac events. In summary, our findings regarding LDL-C levels indicate that lipid lowering therapy today is wholly inadequate.

We find the general practitioner's (GP) role in this interesting. After patients are being discharged from the hospitals, the GPs take over the responsibility of follow-up for the CHD patients. That means that in most cases the GPs are in charge of the prescription of lipid lowering therapy for these patients. We find it especially interesting that prescription of HIST has declined, and that only a small proportion of patients use combination therapy of Ezetimibe and statin, even though the guidelines clearly state that this should be used if guideline levels are not met. We speculate that this might be due to the GPs expecting more information about lipid lowering therapy from cardiologists at discharge from hospitals then they receive today, and that they usually continue the drug prescribed from specialists. It might also be because of it being too much work to familiarize oneself with the specific guidelines, or that it seems risky to try out new therapies. However, knowing that a large proportion of the Norwegian population are in need of lipid lowering therapy, it is important that the GPs know about these guidelines, and use the medication as recommended.

It must be mentioned that the ESC-guidelines also state that recommended target of LDL-C could also be a reduction of at least 50% if baseline levels are between 1,8 and 3,5 mmol/L. We do not have data on how much the LDL-C levels have decreased, due to almost all participants using lipid lowering therapy at baseline. This means that we cannot evaluate this part of the guideline-recommendation.

4.2 The effect of extended CR on the lipid profile

Several blood-lipids had an unfavorably change within one year; mean total cholesterol increased in all groups, significantly within both HBG and CG. LDL-C increased significantly within both HBG and CG and HDL-C decreased significantly within MBG and HBG groups. Triglycerides was the only blood-lipid to have a positively change; it decreased significantly in MBG. Between-group changes were significant for HDL-C and triglycerides.

The results give a slight indication that MBG had more favorable outcomes than the other groups, as it did not have a significant increase in total cholesterol and LDL-C, and triglycerides decreased significantly. However, MBG were the only group with a significant increase of both HIST and Ezetimibe. This might explain the slightly better outcome than the

other groups. In fact, all the significant changes in blood lipids will be difficult to attribute to different interventions, as there has been changes of lipid lowering therapy in all groups.

These results are in line with the findings in another study looking at the lipid profile in patients with extended CR versus standard CR[26], which found a favourable effect on triglycerides levels in the extended group, and no difference between groups in total cholesterol and LDL-C levels. However, that study also found extended CR to lead to higher HDL-C levels, which is not the case in our study. An RCT[77] found total cholesterol levels to improve slightly when CR was extended with counselling sessions versus standard CR. Another RCT[30] found no additional effect from extended CR on cholesterol outcomes. This shows that the findings are inconsistent. Overall, extended CR does not seem to have any considerable additional effect on the lipid profile.

It is noteworthy that taking all participants into account, both total cholesterol and LDL-C have increased significantly within one year. The same trend is found in an RCT comparing extended follow-up to standard CR[30]. It is especially a concern that this has happened relatively short time after index event and after having completed standard CR, when patients have had more closely monitoring than they will have onwards. This is also happening despite the high prescription rate of lipid lowering therapy and the high level of PA in patients. Considering all the evidence that elevated LDL-C lead to a higher-risk of cardiac events and cardiac mortality, this trend is of especially concern. However, as mentioned before, the prescription rate of HIST have decreased between baseline and 1-year, which could explain the unfavorable trend.

It is difficult to evaluate the effect of PA on blood lipids in this study, as the level of PA was high at both baseline and 1-year. However, we can compare our results the ones from EUROASPIRE V and NOR-COR, which both found considerably higher amount of inactivity. NOR-COR had quite similar LDL-C outcomes as our study, but our participants have a much higher level of PA. EUROASPIRE V had an overall higher LDL-C level, but the proportion of patients on HIST compared to our study was lower. Thus, one could assume that a high level of PA does not have any effect on LDL-C or the lipid profile in general, and in addition, comparing these findings suggest that extended CR does not lead to an additional effect on the lipid profile. In our study there was found no association between level of PA

and both LDL-C levels and triglyceride levels. This would be expected as level of PA were overall very high.

4.3 Levels of triglycerides

Almost all participants reached recommended target level of triglycerides of ≤ 1,7 mmol/L, as overall mean triglyceride level was below target at 1-year follow up. This differs from levels found in a similar study[78], where mean triglyceride level was found to be 1,81mmol/L. Statins is found to lower triglycerides[44], which might explain the high level of adequate triglyceride-control found in our study. In addition, exercise seems to positively affect triglycerides levels[38,39], and considering the high level of PA in our participants, it is likely that it has contributed to the overall low triglyceride-levels. However, it is difficult to evaluate the effect from exercise in our study, since the participants were very physically active at both baseline and at 1-year follow-up.

4.4 The level of PA and the effect of extended CR

Most participants achieved guideline level of moderate PA ≥ 150 minutes per week. Previous studies have implied that 60-66% of patients with established CHD are not reaching recommended level of PA[24,66], which is not in line with our findings. On the other hand, two recent studies have similar outcomes as ours when it comes to maintenance of PA after CR[79,80]. It is important to consider that all the participants have previously completed on average 12 weeks of CR before being included in this study. We do not know if the high level of PA is due to participants being more active than the population in general, or if their exercise habits have changed due to participating in standard CR.

There is a significant difference between groups in change of time in moderate PA. Both MBG and HBG have significantly decreased in time of moderate PA. The CG stay more active than both intervention groups. The proportion of participants in the CG group that does not meet recommendations for moderate PA, is lower in CG than in both MBG and HBG. In contrast to our findings, studies have implied that extended CR leads to higher maintenance of PA-level compared to standard CR only[28-30]. However, all groups achieve PA-levels far above recommended target, so the differences between groups probably does not have any clinical importance. However, our findings might indicate that extended CR is not superior to standard CR in developing a physically active lifestyle.

As for gender, men are significantly more active than women. Almost all men have an adequate PA level, and there are less women who reach recommended target. First, it is important to look at the quite large standard deviation found in the calculations of means. This indicates that there are great differences between individuals, in that some participants are very active, and some are almost completely inactive. Secondly, the included number of women in this trial is quite small, which might mean that our results are not applicable for women in general. However, our difference between gender are similar to those found in a study from 2016[81], but the level of moderate PA are much higher for both gender in this study sample.

4.5 Risk factor profiles at baseline

The risk factor profile at baseline in NOR-COR and EUROASPIRE V both differs greatly from our study. NOR-COR reported 43% having hypertension, 17% having DM and 35% smoking. The EUROASPIRE V had higher frequency of smoking (19%) overweight and obesity (82%), DM (29%) and hypertension (95% reported to be on blood pressure lowering treatment) compared to our findings at baseline. Regular PA was lower in both NOR-COR and EUROASPIRE V compared to our population (40% and 34%, respectively).

Considering the baseline differences from both EUROASPIRE V and NOR-COR, one might assume that our participants was healthier than the average CHD population. We find this interesting, as the high level of PA in our participants could have contributed to the low rate of hypertension and DM at baseline. However, the included number of participants was much larger in both of the other studies.

We also find it interesting that there was an higher proportion of participants that had HbA1c levels above 6,5%, which is the threshold for DM according to guidelines[76], than the proportion of participants reporting to have DM at baseline. At 1 year, the proportion with HbA1c levels above 6,5% had slightly increased. This probably means that there are participants with either undiagnosed DM or a newly found DM.

4.6 Study strengths and weaknesses

There are several strengths with our study. First, it is an RCT, which is considered gold standard for research. Secondly, the sample size is fair, with a small drop-out rate (7,4%). The participants were randomly allocated. Data on adherence are powerful evidence considering the method of data collection.

There are certain limitations with our study. First, the population was mostly men, and median age was quite low, which might limit the generalizability with the study. Moreover, the level of PA was only measured for one week at both baseline and 1-year follow-up. There is a possibility that the participants had higher activity levels during the time of measurement than they normally have, and this must be considered when looking at the results for PA. There might also be a volunteer bias as participants who choose to enroll in exercise-trials tend to be more exercise-motivated. One could also speculate that these participants are more adherent to drugs than those refusing to participate. This must be taken into account when interpreting these results.

4.7 Clinical relevance and future studies

Regarding the possible clinical relevance of our research, our findings might affect the work of both cardiologists and GPs, as we highlight the significance of reaching LDL-C target level and following guidelines regarding lipid lowering therapy. Standard CR seems to be sufficient for participants to maintain an adequate level of PA, which underlines the importance of it being offered and available to all CHD patients.

Future studies should include more women and elderly, as it is already known that they are underrepresented in CR. We also need studies investigating if Ezetimibe combined with statins and PCSK9 inhibitors are both safe and efficient in a long-term perspective compared to HIST.

5.0 Conclusion

Our findings indicate that current lipid lowering therapy in patients with CHD is inadequate, despite good adherence. We suggest that a larger proportion of patients should be using HIST, Ezetimibe combined with statins or PCKS9 inhibitors to lead to further reductions in LDL-C. Extended CR was not found to have any additional effect on the lipid profile. The level of PA has not improved from baseline to 1-year follow-up, thus extended CR was not found to lead to higher maintenance of PA. Standard CR seems sufficient to lead to adequate level of PA in patients with CHD.

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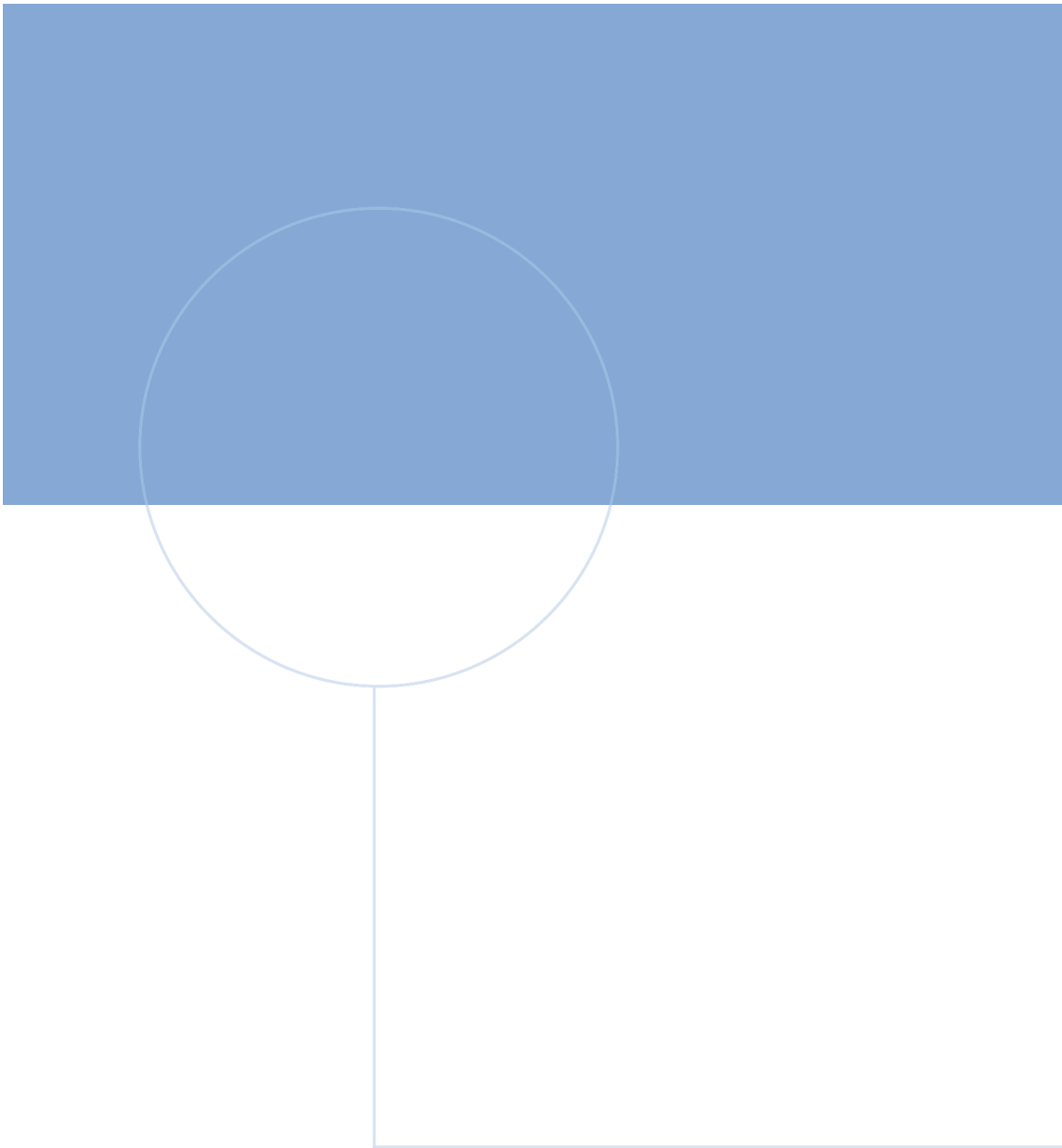

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