2015•2016
FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN
master in de revalidatiewetenschappen en de kinesitherapie

Masterproef

The clinical impact of bèta-blocker intake on fat mass and BMI in patients with cardiometabolic disease following an exercise training program

Promotor :
Prof. dr. Dominique HANSEN

Joren Jacobs , Bart Peuters
Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie

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Title: Interactions between cardioprotective drug intake and training effects during cardiovascular rehabilitation:

Master Thesis Part 2: The clinical impact of bèta-blocker intake on fat mass and BMI in patients with cardiometabolic disease following an exercise training program.

New findings

(1) What is the central question of this study?

Is there an impact of bèta-blocker intake on adipose tissue mass and BMI change in patients with cardiometabolic disease following an exercise training program?

(2) Hypothesis?

It is hypothesized that bèta-blocker use suppresses adipose tissue mass reduction.

(3) What is the main finding and its importance?

We did not found a significant impact of beta-blocker therapy on changes in adipose tissue mass and BMI in revascularized coronary artery disease patients taking bèta-blockers or not, although subjects with a BMI higher than 35 kg/m^2 experienced smaller decrements in BMI when taking bèta-blockers during exercise training intervention. Due to the many limitations of our study, further research seems necessary to make conclusions about the possible clinical effect of beta-blocker intake on adipose tissue mass and BMI.

MSc Students: Jacobs Joren, Peuters Bart

Promotor: Prof. Dr. Hansen Dominique
Co-promotor: Prof. Dr. Dendale Paul

Research framework

The Rehabilitation and Research center of the Biomedical Research Institute of Hasselt University (REVAL) and their research group, focus on the different domains of the Rehabilitation Sciences and Physiotherapy (Neurologic, Musculoskeletal, Pediatric, Psychological, Cardiac, Vascular, Respiratory and Metabolic rehabilitation). The REVAL researchers study the functional result and underlying biomedical mechanisms of the treatment methods in the different domains. With their fully equipped center and in collaboration with national and international partners (universities, hospitals, research groups,..), they try to extend their expertise in the aforementioned specializations. In this master thesis, within the domain of Cardiovascular and Metabolic disorders, we collaborate with the multidisciplinary Rehabilitation and Health Centre (ReGo) from the Virga Jesse hospital in Hasselt. Prof. Dr. Dominique Hansen, Researcher and Professor in the rehabilitation and exercise physiology in internal disorders at the faculty Medicine and Life Sciences of Hasselt University, promotes this master thesis.

MASTER THESIS PART 2

Abstract

Background:

The recommended pharmacological treatment for hypertensive patients with metabolic syndrome (obesity) and cardiovascular disease includes bèta-blockers. Despite an *in vitro* inhibitory impact of bèta-blocking agents on adipocyte lipolysis, the clinical effect of bèta- blocker intake on adipose tissue mass and BMI (during an exercise training intervention) in patients with cardiometabolic disease remains to be studied.

Purpose of research:

The aim of this research was to examine whether the use of bèta-blockers affects changes in adipose tissue mass and BMI in cardiometabolic patients during an exercise training intervention.

Method:

In the first study cohort, 38 re-vascularized patients (CABG, PCI/PTCA, Endo-CABG, Endo-ACAB) followed a 7-week exercise training intervention. Whole-body adipose tissue mass was measured at baseline and after 7 weeks by bio-electrical impedance analysis (BIA). The difference in change in adipose tissue mass was compared between subjects who took bèta-blockers (n= 26) versus subjects who did not (n=12). In the second study cohort, 221 obese and overweight subjects followed an exercise training intervention, combined with a diet, for 21(±7,45) weeks. BMI was measured at baseline and end of the program. The change in BMI was compared between subjects that took bèta-blockers (n=46) and those who did not (n=175). We also divided this group in subgroups of patients with a BMI lower or equal to 35 kg/m^2 (n= 111) or with a BMI higher than 35 kg/ m^2 (n=110).

Results:

Despite significant improvements in exercise capacity in revascularised coronary artery disease patients (change in VO2 peak/kg; 1,568±3,21ml/kg/min, p=0,005) and maximal power output (change in peak cycling power output; 17±13 Watt; p=0,000) we found no significant change in BMI (kg/m^2) and adipose tissue mass (kg) in total group. There were no differences in change in adipose tissue mass (p= 0,545, -0,10±2,70 vs -0,44±1,32 kg), % adipose tissue mass (p= 0,505, -0,09±2,43 vs -0,53±1,12 %), BMI (p=0,447, -0,03±0,86 vs -0,06±0,67 kg/m2), body weight (p=0,485, 0,06±2,97 vs -0,18±2,10 kg) between groups (controls vs. patients on bèta-blocker therapy, respectively). As result of the intervention in the obese cohort, the BMI in total group of obese an overweight subjects declined significantly (change by -2,7±2,4 kg/m2, p<0,001), without a significant difference between groups (-2,3±2,35 vs -2,9±2,43 kg/m2, p=0,055, in patients on bèta-blocker therapy vs.

controls, respectively). However, within subjects with a BMI > 35 kg/ m^2, we found a significant smaller decrease in BMI in the bèta-blocker group in comparison with the subjects that did not take bèta-blockers (-2,6±2,8 vs -3,6±2,9 kg/ m^2, p=0,031, in controls vs. patients on bèta-blocker therapy, respectively).

Discussion and conclusion:

We did not found a significant impact of bèta-blocker therapy on changes in adipose tissue mass and BMI in revascularized coronary artery disease patients taking bèta-blockers or not, although subjects with a BMI higher than 35 kg/m^2 experienced smaller decrements in BMI when taking bèta-blockers during exercise training intervention. Due to the many limitations of our study, further research seems necessary to make conclusions about the possible clinical effect of beta-blocker intake on adipose tissue mass and BMI.

Keywords:

Adrenergic bèta-antagonists, Bèta-blockers, Bisoprolol, Nebivolol, Metoprolol, Propranolol, Celiprolol. Adipose tissue, Fatmass, Body-mass index, Body composition, Body Weight, Exercise capacity, Exercise, Cardiometabolic disease, Hypertension, Cardiovascular disease, Coronary artery disease, Coronary heart disease, Previous myocardial infarct, PCI, CABG, Endo- ACAP, Endo-CABG, Metabolic syndrome, Obesity.

Introduction

Following the guidelines for the management of arterial hypertension by the European society of cardiology (ESC) antihypertensive drug treatment is recommended when total cardiovascular risk is high, such as in hypertensive patients with (pre-) diabetes (type 1 and 2), cardiovascular disease and metabolic syndrome (obesity) [1]. Lowering blood pressure by pharmacological treatment, in parallel to life style changes such as regular physical exercise and healthy diet, is associated with important reductions in cardiovascular event incidence. (Class, level A) The recommended pharmacological treatment strategy and choice of drugs include bèta-blockers as monotherapy or in combination with diuretics, calcium antagonists, ACE-inhibitors and angiotensin receptor blockers. (Class 1 Level A) Despite more reported side-effects (impaired glucose tolerance and impaired insulin sensitivity) as result of intake of bèta-blockers as opposed to other drug classes, bèta-blockers are still often prescribed to patients with cardiometabolic diseases [5,6,7,8]. (Class 1, level A) (For class and level, see appendix 1)

Adiposity, especially white adipose tissue accumulation, is related to a greater cardiovascular event risk, due to its blood pressure elevating effect. It thus follows that in patients with hypertension reductions in adipose tissue mass should be aimed at. However, most bèta-blockers exert an inhibitory effect on adipose tissue lipolysis, at least *in vitro*, partly due to the blocking effect on the bèta - receptors (for catecholamines) on the membrane of the adipocytes. In figure 1 the names and types of bèta-blocker and their (most often *in vitro*) effect on adipocyte lipolysis is displayed. Except for nebivolol, celiprolol, esmolol, carvedilol and labetalol, all bèta-blockers blunt lipolysis in these studies. Nebivolol seemed to stimulate lipolysis, because of the hypothesized agonist effect on beta-3 receptors, but studies reported contradictory results about the existence of this receptor [31]. The blunting effect of atenolol, metropolol, pindolol, propranolol were not yet confirmed.

Beta blocker	Type	Lipolysis	Reference
Acebutalol	**Selective (Bèta 1)**	↓	**13**
Atenolol	**Selective (Bèta 1)**	↓ **or =**	**10, 12, 14, 15, 16**
Betaxolol	**Selective (Bèta 1)**	↓	**13**
Bisoprolol	**Selective (Bèta 1)**	↓	**12**
Celiprolol	**Selective (Bèta 1)**	**?**	**-**
Esmolol	**Selective (Bèta 1)**	**?**	**-**
Metoprolol	**Selective (Bèta 1)**	↓ **or =**	**15**
Nebivolol	**Selective (Bèta 1)**	↑	**18**
Pindolol	**Non-selective (1+2)**	↓ **or =**	**9, 17**
Propanolol	**Non-selective (1+2)**	↓ **or =**	**10, 11**
Carvedilol	**Alfa 1 - Bèta**	**?**	**-**
Labetalol	**Alfa 1 - Bèta**	**?**	**-**

Fig 1: Effect of bèta blocker on adipocyte lipolysis

↓ Decrease (or complete blunting for lipolysis)
↑ Increase
= No effect reported ? Unknown

Because of the possible blunting effect of bèta - blocker intake on adipocyte lipolysis, it remains to be studied whether bèta-blocker intake affects changes in adipose tissue mass and BMI in patients with cardiometabolic disease who follow an exercise training intervention or diet. Both short and long-term endurance training makes adipocytes more sensitive to catecholamine stimulation[31], but it remains uncertain whether bèta-blocker intake has a clinical impact on change in adipose tissue mass.

The aim of this study was to examine whether the intake of bèta-blockers affects changes in adipose tissue mass and BMI in cardiometabolic disease patients during an exercise training intervention. It was hypothesized that beta-blocker intake suppresses adipocyte lipolysis and, as a result, lowers adipose tissue mass reduction in cardiometabolic disease patients.

Methods

3.1 Ethical Approval

This study was approved by the local medical ethical committee (Jessa Hospital, Hasselt, Belgium). In the prospective study all the participants signed an informed consent, stating the aim and protocol of the study. The retrospective study was approved without need for informed consents.

3.2 Subjects

3.2.1 Selection criteria

In the first study cohort we included coronary artery disease (CAD) patients who underwent coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), endoscopic atraumatic coronary artery bypass (endo-ACAB) and endoscopic coronary artery bypass graft (endo-CABG) and started an ambulatory exercise training program. Revacularized patients who used diuretics, insulin or changed bèta-blocker therapy, during the 7 weeks of follow up, were not included. For the second cohort overweight and obese patients following an exercise training program as part of a weight reduction program were included. Patients using exogenous insulin in stead of other oral diabetic drugs were not included. Furthermore, we excluded all the patients who did not underwent a second BIA or body weight measurement, in both the first and the second cohort.

3.2.2 Participants / Subjects

In the first study cohort our target subjects were PCI and CABG patients who started a 12 week (3 months) exercise training intervention (preceded by a bio-electrical impedance analysis (BIA) and a Cardiopulmonary exercise test (CPET) at the Regional Rehabilitation and Health Centre (ReGo) from the Jessa hospital in Hasselt. From the start of our data collection (1/9/16) till the deadline (25/04/16), 89 PCI, CABG, Endo-ACAB and Endo-CABG patients started a cardiac rehabilitation program. Due to restenosis there was one drop out and we also excluded one patient who stopped bèta- blocker intake during follow-up. After approximately 7 weeks there was a follow up BIA and CPET. 36 subjects did not undergo a second BIA and CPET measurement before the data collection deadline. Because of the lipogenic/adipogenic effect of insulin and the influence of diuretics on fluid balance (and thus also BIA) we decided to exclude the patients who used these types of medication[19,20,21]. Data from 38 subjects were analysed. 26 patients took bèta-blockers and 12 patients did not (see fig. 2).

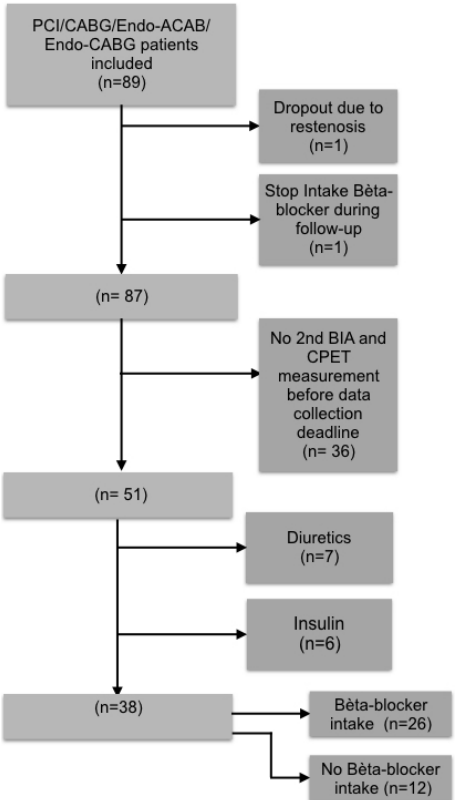


Fig. 2: Study flowchart prospective cohort (PCI/ CABG patients)

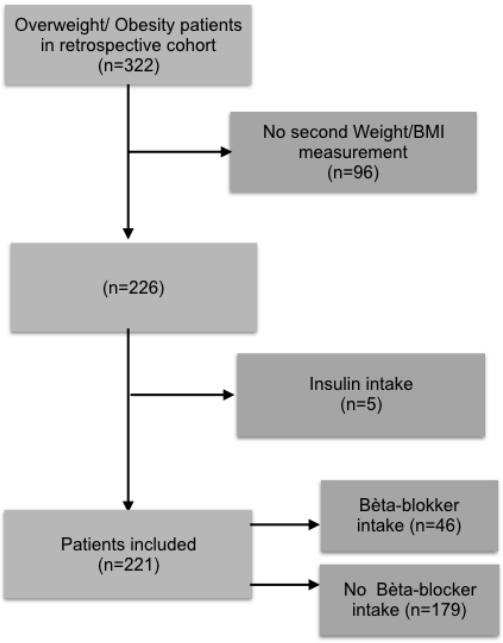
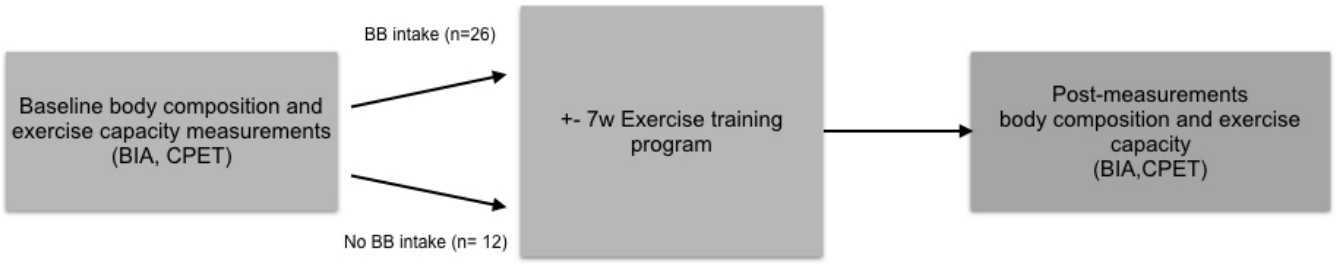


Fig. 3: Study flowchart retrospective cohort (Obesity and overweight patients)

In the second study cohort 322 obese and overweight patients, who followed a weight reduction program, were included in the already collected dataset. 96 patients had no second body weight and BMI measurement. Five patients who used insulin instead of metformin (mainly because of diagnosis of type 1 instead of type 2 diabetes) were excluded due to the possible lipogenic/adipogenic effect of insulin[19,20,31]. Obese and overweight patients who used metformin were not excluded because metformin increases insulin sensitivity and has no effect on blood insulin levels. Data from 221 obese and overweight subjects were analyzed, 46 patients took bèta-blockers and 175 patients did not (see fig. 3 above).

3.2.2 Design

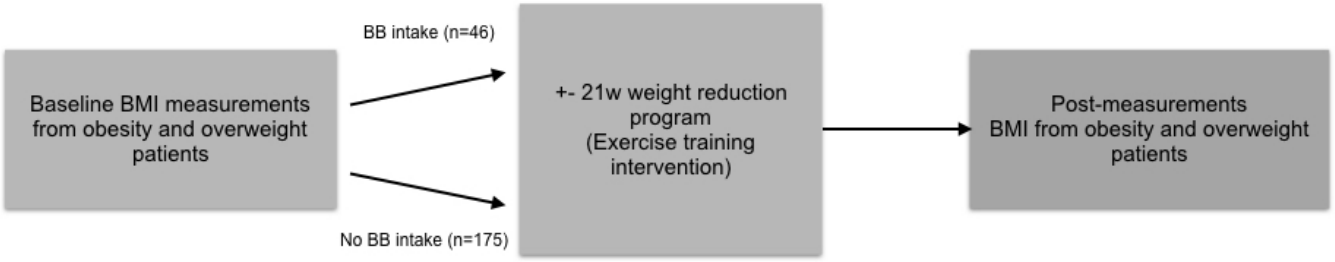
The study design of the first cohort was a prospective observational (cohort) study with CABG, PCI, endo-ACAB and endo-CABG patients taking bèta- blockers compared with patients not taking bèta- blockers (see fig. 4).



BIA= Bio-electrical Impedance analysis, CPET= Cardiopulmonary exercise test, BB= Bèta Blocker

Fig. 4: Prospective observational study design (Cohort 1: PCI/ CABG patients)

For the second study, we also used an already collected dataset for a retrospective observational cohort study of obese and overweight patients who followed an exercise training program whether or not combined with bèta-blocker intake (see fig. 5).



BMI= Body Mass Index (kg/m^2), BB= Bèta blocker

Fig.5: Retrospective observational study design (Cohort 2: Obesity patients)

3.3 Outcome Parameters

3.3.1 Primary (dependent) outcome measure

In the prospective cohort the primary outcome variable was whole-body adipose tissue mass (kg).

In the retrospective cohort primary outcome variable was BMI (kg/m^2).

3.3.2 Explanatory (independent) variable

The explanatory (independent) variable in the prospective and the retrospective cohort was the intake of bèta-blockers (whether or not) during the intervention.

3.3.3 Secondary outcome measures

In the prospective cohort the secondary outcome variables were fat percentage, BMI, bodyweight, peak VO2/kg, peak METS, peak VO2, peak watt, peak watt/kg, peak RER, absolute fat-free mass and fat-free mass percentage.

3.3.4 Possible confounding variables

In both studies exercise program duration and the number of exercise sessions was also taken into account. Because of the possible confounding effect of use of other types of medication we also collected these data in the prospective cohort. In the retrospective obesity cohort these data were not collected.

3.3.5 Other variables

Next to type of treatment (PCI, CABG, Endo-ACAB, Endo-CABG) after coronary artery disease (CAD) we also collected sex, age and body length of the subjects at baseline.

3.4 Materials and Methods (Measurements)

3.4.1 Bio-electrical impedance analysis

Despite a lack of validity of the device for the follow-up of change in adipose tissue mass in cardio-metabolic disease patients we were obliged to use the “TANITA TBF 300”, a lower body bio-electrical impedance analyzer. Gupta ea. and Vedich ea. reported a good comparison for measurement of changes in % adipose tissue mass within the same group [28,29]. Additionally BIA is the most practical method for the measurement of body composition because it is easy in use, accessible, time efficient and not expensive. [29]. The height, necessary for the adipose tissue mass estimation by BIA, was measured using a calibrated height scale.

3.4.2 Cardiopulmonary exercise test (CPET)

Subjects performed a cardiopulmonary exercise test on an electronically braked cycle (Ergofit GmbH & Co. Pirmasens, Germany), as executed in previous studies[34]. The cycling frequency was set at 70 cycles/min and the test ended when the patient failed to maintain a pedal frequency of at least 60 cycles/min. Additionally, the exercise tests ended prematurely when myocardial ischemia and or severe ventricular arrhytmias occured (detected by ECG or symptomatically). Both the starting and incremental cycling resistance was set between 10 and 40 watt and will increase every minute. Pulmonary gas exchange analysis was performed by using cardiopulmonary ergospirometry device (Schiller CS200, Schiller AG, Switzerland). Before every test, a gas and volume calibration was executed. During the tests environmental temperature was kept stable (19-21°C). Oxygen uptake (VO2), Expiratory volume (VE) and respiratory exchange ratio (RER) was collected breath-by-breath and averaged every 10 seconds. In Addition, maximal cycling resistance (Wpeak) and total test duration was reported. The first (VT1) and second ventilatory thresholds (VT2) were calculated by respectively the V-slope and the VE/VCO2 slope method [22].

3.5 Intervention

The treated CAD subjects followed a 7(±2,63) -week endurance exercise training intervention, 3 times a week with a session duration of 45 minutes (walking, cycling, arm cranking) with an intensity between first and second ventilatory threshold. There was no standard diet or strength exercise training included in the program. The overweight and obesity patients followed a 5 (±1,7) month exercise training intervention (with an additional diet program), 3 times a week, whether or not combined with beta-blocker use with an intensity between first and second ventilatory threshold.

3.6 Statistical Analysis

Statistical analysis were executed using SPSS version 23.0 (SPSS Inc., Chicago, IL, USA). Shapiro Wilk tests showed that in both cohorts most data were not normally distributed. Therefore non-parametric test were applied and data were expressed as the mean (SD). In the first cohort the overall changes in whole-body adipose tissue mass (kg), fat percentage, BMI, weight, peak vo2/kg, peak METS, peak Watt, peak Watt/kg, peak RER, fat-free mass (kg) and fat-free mass (%) during follow-up were analyzed by the Wilcoxon signed ranks tests. In the second cohort the overall changes in BMI and body weight were also analyzed by the Wilcoxon signed rank test. For the interaction effect of bèta-blocker intake (whether or not) we used the Mann-Whitney U Test in both cohorts. We also controlled if the bèta-blocker and the control group (no bèta) were matched for all subject characteristics collected at baseline. Therefore we used the Mann-Whitney U or the Fischer exact tests. Next, a forward stepwise multivariate linear regression model was constructed to examine relationships between changes in absolute whole-body adipose tissue mass (first cohort), changes BMI (second cohort) and baseline parameters (age, sex, length, weight, adipose tissue mass, fat-free mass, peak VO2max/kg, peak METS, peak watt, peak watt/kg, peak RER, type of beta blocker, other medication, type of intervention, number of sessions, program duration). A multivariate linear regression model was created, in which relationships between changes in absolute whole-body adipose tissue mass (cohort 1), changes in BMI (cohort 2) and detected independent predictors from the forward stepwise multivariate regression model were examined. Finally, we also divided the obese and overweight group in a subgroup with a BMI lower or equal to 35 kg/m^2 and a subgroup with a BMI higher than 35 kg/m^2. In these subgroups we also controlled if the bèta-blocker group and the control group were matched for all subject characteristics at baseline. Therefore we used the Mann-Whitney U or the Fischer exact tests. For the interaction effect of bèta-blocker intake (whether or not) in both groups we used the Mann-Whitney U Test in both subgroups. Statistical significance was set at $p < 0,05$ (2-tailed).

Results

4.1 Subject characteristics

In the first cohort 38 patients were included (6 females; mean age 61 (±11,5) years; see table 9). 30 subjects were revascularized by PCI, 5 by CABG, 4 by Endo-ACAB and 1 by Endo-CABG. The following medications were taken at baseline: Ca- antagonists (n=7), ACE-inhibitors (n= 14), A2-RA (n=3), anti-coagulants (n=37), statins (n=35), fibrates (n=1), nitrates (n=6), anti-arrhytmics (n=1), thyroxin (+) (n=1), alfa-1-blockers, (n=1) and SSRI's (n=1). From the 38 patients, 26 patients used bèta-blockers (bisprolol (n=23), nebivolol (n=3)) and 12 did not. At baseline the bèta- blocker group (5 females, mean age 60(±11) years) had a mean absolute whole-body adipose tissue mass of 21,76 (±9,29) kg and a BMI of 27,12 (±4,92) kg/m^2. The control group (1 female, mean age 63,42 (±12,77) years) had a mean adipose tissue mass of 21 (±3,84) kg and a BMI of 27 (±2,1) kg/m^2 (For all subject characteristics see appendix 6). We found a significant between-group difference for VO2/kg peak (bèta (19,4 ml/kg/min), control (24,1 ml/kg/min), p=0,03), METs (bèta- (5,54), control (6,89), p=0,03), Watt peak (bèta- (133 watt), control (153 watt), p=0,025) Watt/kg peak (bèta- (1,57 watt/kg), control (2,01 watt/kg), p= 0,021) and the number of obese (BMI≥30) subjects (bèta- (n=7), control (n=1)) next to the difference in bèta-blocker intake (p= 0,000) (See appendix 6).

In the second cohort 221 patients were included (152 females, mean age 51(±13,87); appendix 7). From the 221 subjects, 46 subjects used bèta-blockers and 175 did not. At baseline the bèta- blocker group (31 females, mean age 56 (±12,25)) had a mean BMI of 36 (±5,49) kg/m^2. The control group (121 females, mean age 49 (±13,9)) had a BMI of 34,7 (32) kg/m^2. Next to the difference in bèta-blocker intake (p=0,000) age was not matched between both groups (p=0,003) (See appendix 7). Finally, we also divided the obese and overweight group in a subgroup with a BMI lower or equal to 35 kg/m^2 (n= 111) and a subgroup of patients with a BMI higher than 35 kg/m^2 (n=110) (See appendix 7).

4.2 Overall effect of exercise intervention

In the first cohort we found a significant improvement in peak VO2/kg (p=0,005), peak METs (p=0,005), peak Watt (p=0,000) and peak Watt/kg (p= 0,000) after 7 weeks (mean) of exercise training. Although these results indicate that the exercise training intervention was effective, we did not observe a significant decrease in whole-body adipose tissue mass (p=0,677), percentage body fat (p=0,451), BMI (p= 0,790) and bodyweight (p=0,883) or a significant increase in absolute (p= 0,123) and percentage (p=0,361) fat-free mass (See table 1 and appendix 2).

		PRE	POST	DELTA	P-value
FM(kg)	*Mean*	21,500	21,297	-0,205	0,677
	Median	21,700	21,000	-0,050	
	Std. Dev.	±7,930	±7,363	±2,339	

Table 1: Primary outcomes cohort 1: overall effects; FM= Fat Mass

In the retrospective cohort we found a significant reduction in BMI (p=0,000) and body weight (p=0,000) after a 5 month (mean) weight reduction program (See table 2 and appendix 3).

		PRE	POST	DELTA	P-value
BMI	*Mean*	35,680	32,930	-2,755	**0,000**
	Median	35,000	32,200	-2,400	
	Std. Dev.	±5,695	±5,551	±2,421	

Table 2: Primary outcomes cohort 2: overall effects; BMI= Body Mass Index

4.3 Interaction effect (group*intervention)

In the first cohort we found no significant differences in changes in primary outcomes and secondary outcomes between the bèta- blocker intake group and the control group (no bèta-blocker intake). Thus there was no difference in change in whole-body adipose tissue mass (p= 0,545), % adipose tissue mass (p= 0,505), BMI (p=0,447), body weight (p=0,485) and the other secondary variables (See table 3, figure 6 and 8 and appendix 4).

		PRE		POST		DELTA		P-value
		Bèta	*No Bèta*	*Bèta*	*No Bèta*	*Bèta*	*No Bèta*	
FM(kg)	*Mean*	21,760	20,950	21,662	20,510	-0,096	-0,442	
	Median	22,000	20,250	21,650	19,950	-0,150	-0,550	0,545
	Std. Dev.	±9,293	±3,840	±8,530	±4,004	±2,701	±1,317	

Table 3: Primary outcomes cohort 1: interaction effects; FM= Fat Mass

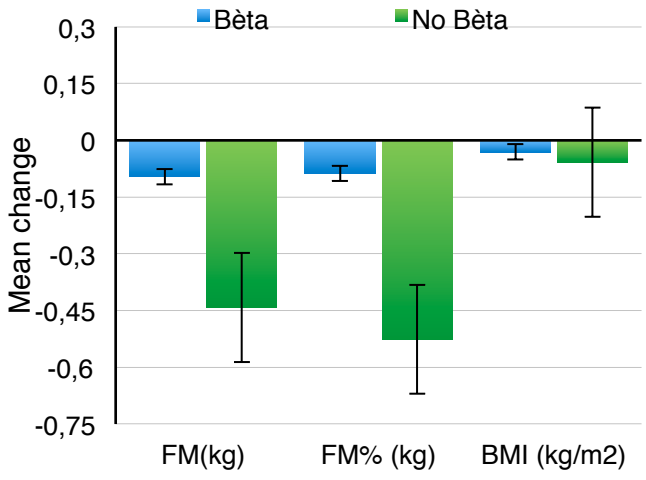


Fig. 6: Difference in changes (mean) in revascularised coronary artery patients; Statistical Significance (Sign.) was set at p < 0,05

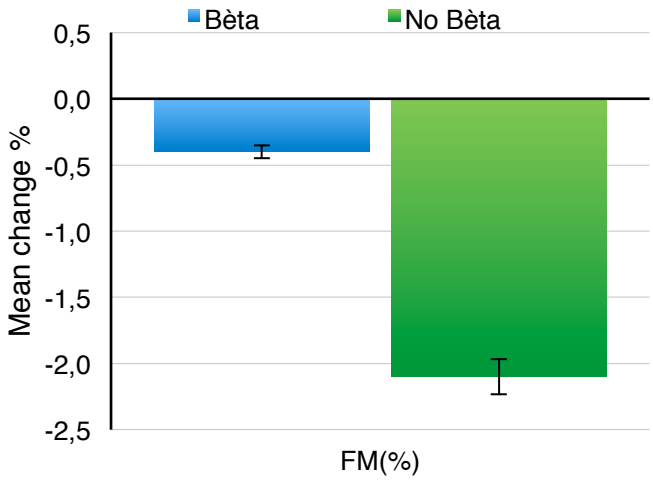


Fig 8: Difference in changes (%) in revascularized coronary artery patients: Statistical Significance (Sign.) was set at p < 0,05

(2) In the second cohort we found no significant, but a trend for a, smaller decrease (p= 0,055) in BMI and body weight in the bèta- blocker group in comparison with the subjects that did not take bèta-blockers (See table 4, figure 7 and 9 and appendix 5).

		PRE		POST		DELTA		Interaction effect
		Bèta	*No Bèta*	*Bèta*	*No Bèta*	*Bèta*	*No Bèta*	
BMI	*Mean*	36,030	35,590	33,680	32,730	-2,348	-2,862	
	Median	35,900	34,700	32,750	31,700	-1,700	-2,400	0,055
	Std. Dev.	±5,493	±5,758	±5,547	±5,551	±2,351	±2,434	

Table 4 : Primary outcomes cohort 2: interaction effects; BMI= Body Mass Index

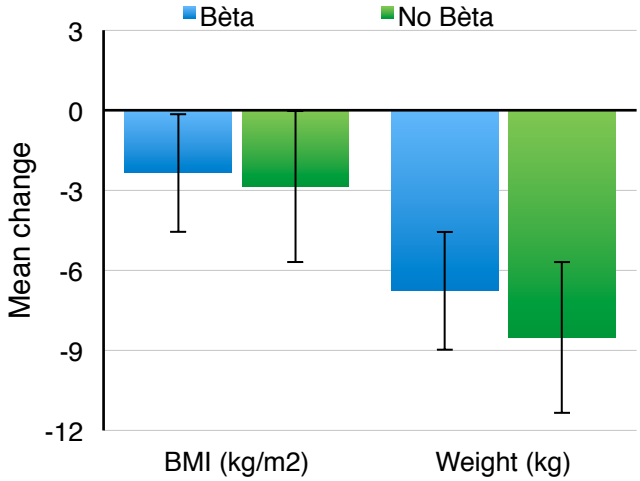


Fig. 7: Difference in changes (mean) in overweight and obese subjects; Statistical Significance (Sign.) was set at p < 0,05

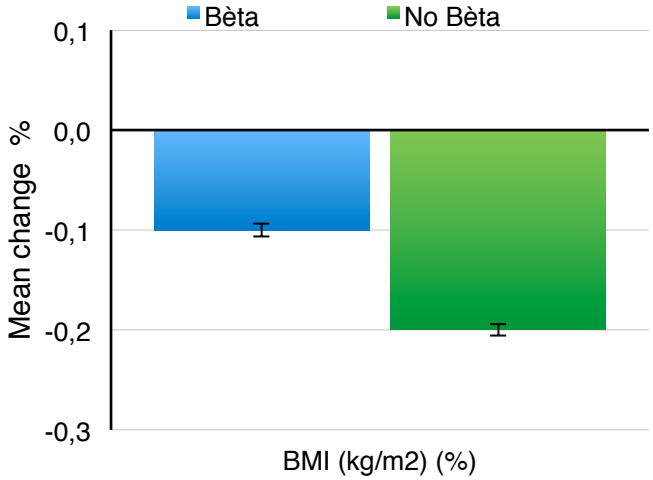


Fig. 9: Difference in changes (%)in overweight and obese subjects; Statistical Significance (Sign.) was set at p>0,05

4.4 Regression analysis

In the first cohort a higher whole-body adipose tissue mass at baseline (β= - 0,326, p= 0,046) was independently related to a greater reduction in whole-body adipose tissue mass (model adjusted r^2 = 0,106, p= 0,046) (See table 5). No other predictors were found.

In the second cohort a higher BMI at baseline (β= - 0,252, p= 0,000) and a longer program duration (β= - 0,260, p= 0,000) were independently related to a greater reduction in BMI (model adjusted r^2 = 0,139, p=0,000) (See table 5). No other predictors were found.

Predictors	r^2	β	Sign.
Delta FM(kg) (Cohort 1)			
FMstart	0,106	-0,326	0,046
Delta BMI (Cohort 2)			
BMIstart	0,072	-0,252	0,000
Duur training (w)	0,076	-0,260	0,000

Table 5: Multivariate Linear Regression

4.5 Interaction effect BMI subgroups (BMI ≤ and > 35 kg/m^2)

We also divided the obese and overweight group in subgroups of patients with a BMI lower or equal to 35 kg/m^2 (n= 111) and a subgroup of patients with a BMI higher than 35 kg/m^2 (n=110). We found a significantly smaller decrease (p=0,031,40,3%) in BMI in the bèta-blocker group in comparison with the subjects that did not take bèta-blockers in the second subgroup (BMI > 35 kg/m^2), but we did not find this significantly smaller decrease (p = 0,409, 8,5%) in the subgroup with a BMI equal or lower than 35 kg/m^2 (See table 6, figure 10 and 11 and Appendix 8, 9).

		BMI < or = 35			BMI > 35	
Delta BMI	**Total (n=111)**	**Bèta (n=20)**	**No Bèta (n=91)**	**Total (n=110)**	**Bèta (n=26)**	**No Bèta (n=84)**
mean (range)	-2,245 (9,3)	-2,055 (6,4)	-2,287 (9,3)	-3,365 (14,3)	-2,573 (10,5)	-3,610 (14,3)
% difference		-6,5%	-7,4%		-6,5%	-9,0%
median	-2,100	-1,600	-2,200	-2,600	-1,700	-2,950
Std. Dev.	±1,638	±1,594	±1,653	±2,892	±2,810	±2,889
P-value Bèta vs No Bèta	0,409			0,031		
% difference Bèta vs No Bèta	8,5%			40,3%		

Table 6: Interaction effects BMI subgroups

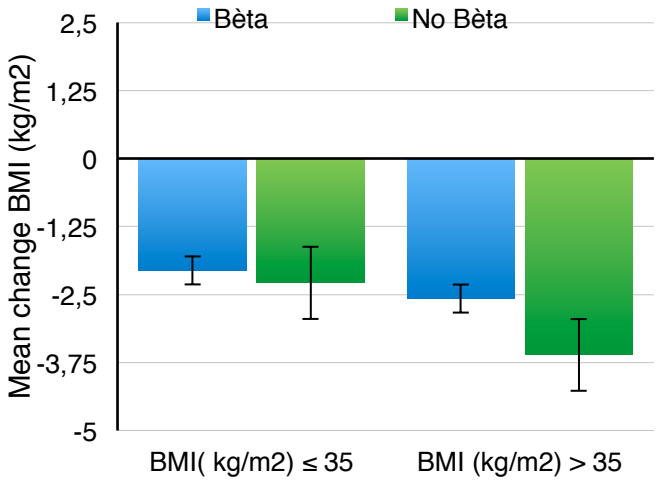


Fig. 10: Difference in changes (mean) BMI subgroups; Statistical Significance (Sign.) was set at p < 0,05

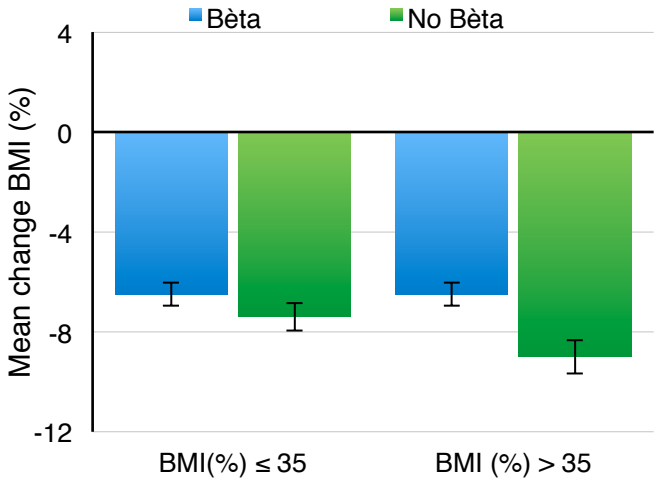


Fig. 11: Difference in changes (%) BMI subgroups; Statistical Significance (Sign.) was set at p <0,05

Discussion

In this study we examined whether the intake of bèta-blockers affects changes in adipose tissue mass and BMI in cardiometabolic disease patients during an exercise training intervention. Although we found a significant decrease in BMI in the overweight and obese group as result of an exercise training intervention, we did not observe a significant decrease in whole-body adipose tissue mass in patients with coronary revascularization. In addition, we found a significantly smaller decrease in BMI in the bèta-blocker group of patients with a BMI > 35 kg/m^2 in comparison with subjects that did not take bèta-blockers. We did not find this significant lower decrease in the subgroup of bèta-blocker taking patients with a BMI equal or lower than 35 kg/m$^{2.}$

Despite we noted a significant reduction in BMI in the obese subjects, we did not observe a significant decrease in whole-body adipose tissue mass in the revasculariseds coronary artery disease patients. Because a decline of 5-10 percent of initial bodyweight (and thus BMI) is necessary for associated significant health benefits (such as decreased risk for insulin resistance, type 2 diabetes mellitus (T2DM), cardiovascular disease, an improvement in lipid profile, bone metabolism and blood pressure), the significant difference in reduction in BMI of 2,5% seems not clinically relevant [27].

That we did found different results between population in change in adipose tissue mass and BMI can be explained by 1. the longer program duration in the overweight/obese cohort and 2. the additional diet in the overweight/obese group. The overweight/obese group trained for 5 months (mean) while the patients with cardiovascular disease trained only 7 weeks (mean). Previous studies have already indicated that indeed exercise program duration is a predictor for successful fat mas reduction[36]. In addition, and in line with this reasoning, we found that a longer program duration was independently related to a greater reduction in BMI (r^2= 0,076, p<0,01). The exercise training program of the obese and overweight subjects was more focused on body weight reduction and thus they also received an additional diet (caloric intake restriction). Indeed it has been shown that the addition of caloric intake restriction to an endurance exercise training intervention significantly augments adipose tissue mass reduction[35]. In both studies we also found that a higher adipose tissue mass or BMI at baseline were independently related to a greater reduction in respectively adipose tissue mass and BMI (p<0,05). This finding further explains to difference in clinical effectiveness of intervention between cohorts. From these results, it thus follows that in patients with coronary revascularization, we should aim to prolong the exercise intervention duration, but also to systematically incorporate changes in diet or caloric intake restriction, to contribute to greater body weight control. Savage ea. found a low caloric expenditure (270 +- 112 kcal per cardiac rehabilitation exercise session) in coronary artery patients and therefore a little impact on fat mass in the short term [27]. These results may be well in line with our findings.

We found no significant impact of bèta-blocker intake on change in BMI and adipose tissue mass in the total cohort, although a trend for a smaller decrease in BMI in the bèta-blocker group in the overweight/obese group was found (p= 0,055). However, when we further divided the overweight/obese group in subgroups of patients with a BMI lower or equal then 35 kg/m^2 and a BMI higher than 35 kg/m^2, we observed a significantly smaller decrease in BMI in the subgroup with a BMI higher than 35 kg/m^2. It thus follows that the intake of bèta-blocker does affect changes in BMI, but this effect is only noticed in extremely obese individuals. This difference can

possibly be explained by the decreased action of the bèta-2-adrenergic (lipolytic) receptor and the increased activity of alpha-2-adrenergic (anti-lipolytic) effect of catecholamines in obese subjects [31]. Because the most often used bèta-blockers, namely bisoprolol, blocks the other lipolytic bèta-1-adrenergic pathway, we hypothesize this possibly could explain the different findings within the obese group and between the obese and the coronary artery disease group. However, an in vitro study with adipose tissue cells seems necessary to verify this hypothesis. Despite that practice guideline for the management of arterial hypertension recommended the use of celiprolol, carvedilol and nebivolol because of the better blood pressure lowering effects and the less side-effects on insulin sensitivity, bisoprolol was still most often used in the revascularized as well as the overweight and obese group[1]. If further studies confirm that beta-blocker intake does compromise fat mass reduction in extremely obese individuals, they warrant reconsideration of current therapy for arterial hypertension.

Notwithstanding the interesting findings in this study, we need to remark some limitations of our study. 1. Caloric intake and caloric expenditure during daily life was not taken into account, 2. Compliance to bèta-blocker therapy was not monitored, 3. BMI can also be increased in people with an increased FFM (and thus higher body weight) during the exercise training intervention, 4. Certain subject features were not matched between groups, and 5. We used bio impedance analysis (BIA) for follow up of change in fat mass. However, despite body composition measured with BIA differed at individual level from that with the DEXA, BIA seemed valid to measure changes in body composition within a group [28,29]. A leg to leg body analyzer, like the TANITA TBF, seems not as reliable as a whole body analyzer to estimate total body fat in obese subjects [30]. Unfortunately there was no whole body analyzer, available. We also not know whether the measurements were taken in accordance with the recommended guidelines[33]. The best indicator for higher cardiovascular risk concerning type and location of adipose tissue is the percentage of visceral abdominal white adipose. It is clear that we would have liked to collect these data, but regretfully this is not possible with BIA. With the TANITA lower body analyzer we estimated % of total body fat, but we cannot differentiate between % of fat mass in trunk and limbs.[30].

Due to the many limitations of our study, further research seems necessary, For further research we would like to recommend: 1) The use of DEXA or MRI for determination of fat mass, 2) Standardized exercise protocols in intervention and control group (for training volume), 3) Standardization of caloric use and caloric intake (daily), 4) Randomization of subjects, 5) Matched groups and a 6) Higher number of sample size.

Conclusion

We did not found a significant impact of beta-blocker therapy on changes in adipose tissue mass and BMI in revascularized coronary artery disease patients taking bèta-blockers or not, although subjects with a BMI higher than 35 kg/m2 experienced smaller decrements in BMI when taking bèta-blockers during exercise training intervention. Due to the many limitations of our study, further research seems necessary to make conclusions about the possible clinical effect of beta-blocker intake on adipose tissue mass and BMI.

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Appendix 1: Grades of recommendation Practice Guideline EHS/ESC

Table 1 Classes of recommendations

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*	Should be considered
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Table 2 Levels of Evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Appendix 2: secondary outcomes cohort 1: overall effects

		PRE	POST	DELTA	P-value
VO2/kg Peak	*Mean*	21,270	22,839	1,568	**0,005**
	Median	21,250	22,700	1,450	
	Std. Dev.	±4,352	±4,460	±3,212	
VO2 peak	*Mean*	1658,280	1781,000	123,422	
	Median	1699,650	1875,070	133,930	**0,003**
	Std. Dev.	±389,000	±399,875	±241,386	
METS Peak	*Mean*	6,080	6,530	0,448	**0,005**
	Median	6,070	6,490	0,414	
	Std. Dev.	±1,240	±1,270	±0,9176	
W/kg Peak	*Mean*	1,773	1,998	0,225	**0,000**
	Median	1,739	1,970	0,190	
	Std. Dev.	±0,435	±0,483	±0,180	
W Peak	*Mean*	138,550	155,630	17,080	**0,000**
	Median	142,000	156,000	17,000	
	Std. Dev.	±38,639	±40,527	±12,994	
RER Peak	*Mean*	1,250	1,260	0,014	0,279
	Median	1,250	1,280	0,000	
	Std. Dev.	±0,110	±0,096	±0,098	
FFM (kg)	*Mean*	57,070	0,189	-0,205	0,123
	Median	57,950	0,150	0,050	
	Std. Dev.	±9,159	±8,610	±1,936	
FFM (%)	*Mean*	73,175	0,226	-0,226	0,361
	Median	74,349	0,267	-0,267	
	Std. Dev.	±7,390	±6,926	±2,098	
FM(%)	*Mean*	27,050	26,825	-0,226	0,451
	Median	25,773	25,651	-0,267	
	Std. Dev.	±7,390	±6,926	±2,098	
BMI	*Mean*	27,080	27,045	-0,039	0,790
	Median	26,400	20,050	0,000	
	Std. Dev.	±4,203	±4,065	±0,800	
Gewicht	*Mean*	78,390	78,371	-0,016	0,883
	Median	79,100	79,750	0,000	
	Std. Dev.	±12,814	±12,115	±2,697	

Appendix 3: Secondary outcomes cohort 2: Overall effects

		PRE	POST	DELTA	Overall effect
Gewicht	*Mean*	102,611	94,461	-8,150	**0,000**
	Median	98,700	90,500	-6,800	
	Std. Dev.	±22,603	±20,537	±7,560	

Appendix 4: Secondary outcomes cohort 1: Interaction effects

		PRE		POST		DELTA		P-value
		Bèta	*No Bèta*	*Bèta*	*No Bèta*	*Bèta*	*No Bèta*	
VO2/kg Peak	*Mean*	20,300	23,380	21,370	26,033	1,069	2,650	
	Med	19,400	24,100	21,050	26,500	1,200	2,350	0,146
	St. D	±4,476	±3,327	±3,923	±3,957	±3,499	±2,234	
VO2 peak	*Mean*	1564,500	1861,000	1651,900	2062,930	87,393	201, 480	
	Median	1518,920	1928,610	1621,310	2028,770	88,165	191,285	0,207
	St. D	±392,463	±305,159	±370,051	±317,043	±263,928	±167,212	
METS Peak	*Mean*	5,800	6,680	6,100	7,438	0,305	0,757	
	Med	5,540	6,890	6,010	7,571	0,343	0,671	0,146
	St. D	±1,279	±0,950	±1,120	±1,130	±0,990	±0,640	
W/kg Peak	*Mean*	1,678	1,980	1,906	2,197	0,228	0,216	
	Med	1,506	2,008	1,916	2,119	0,213	0,178	1,000
	St. D	±0,447	±0,336	±0,498	±0,399	±0,189	±0,166	
W Peak	*Mean*	129,270	158,670	146,690	175,000	17,420	16,330	
	Med	133,000	153,500	152,000	162,000	18,000	16,000	0,841
	St. D	±37,164	±35,181	±39,160	±37,962	±13,456	±12,471	
RER Peak	*Mean*	1,240	1,280	1,260	1,270	0,025	-0,009	
	Med	1,230	1,300	1,270	1,290	0,500	-0,005	0,395
	St. D	±0,124	±0,055	±0,109	±0,068	±0,102	±0,089	
FFM (kg)	*Mean*	55,950	58,920	56,100	59,180	0,158	0,258	
	Med	56,050	59,300	56,350	59,700	0,100	0,300	0,841
	St. D	±9,613	±8,097	±8,859	±7,995	±2,161	±1,410	
FFM (%)	*Mean*	72,633	73,635	72,720	74,161	0,087	-0,526	
	Med	74,280	74,219	74,259	75,501	-0,068	-0,542	0,525
	St. D	±8,409	±4,719	±7,760	±4,787	±2,428	±1,121	
FM(%)	*Mean*	27,367	26,365	27,280	25,839	-0,087	-0,526	
	Med	25,720	25,781	25,741	24,499	0,069	-0,542	0,505
	St. D	±8,409	±4,719	±7,760	±4,787	±2,428	±1,121	
BMI	*Mean*	27,120	27,010	27,088	26,950	-0,031	-0,058	
	Med	26,500	26,400	26,350	25,950	0,100	-0,150	0,447
	St. D	±4,923	±2,079	±4,689	±2,365	±0,865	±0,672	
Body weight	*Mean*	77,700	79,870	77,770	79,683	0,062	-0,183	
	Med	76,300	81,600	78,850	80,750	0,250	-0,450	0,485
	St. D	±14,385	±8,862	±13,416	±9,051	±2,967	±2,101	

Appendix 5: Secondary outcomes cohort 2: Interaction effects

		PRE		POST		DELTA		Interaction effect
		Bèta	*No Bèta*	*Bèta*	*No Bèta*	*Bèta*	*No Bèta*	
Gewicht	*Mean*	102,011	102,769	95,246	94,254	-6,765	-8,514	
	Median	99,350	98,200	91,000	90,500	-4,300	-7,600	0,055
	Std. Dev.	±20,506	±23,238	±20,419	±20,436	±6,866	±7,631	

Appendix 6: Subject characteristics PCI/CABG cohort at baseline

Subject characteristics at baseline				P-value
	Total (n=38)	No Bèta (n=12)	Bèta (n=26)	
Age (years)	62 (46)	67 (42)	61 (41)	0,146
Sex (n female)	6	1	5	0,643
Weight	79,10 (63)	81,6 (31)	76,30 (63)	0,699
Length	171,00 (26)	173,50 (26)	170,50 (21)	0,233
BMI	26,40 (19)	26,40 (7)	26,50 (19)	0,792
Obesity (BMI > 30)	8	1	7	**0,036**
Bisoprolol (n)	23	0	23	**0,000**
1,25 mg (n)	1	0	1	1,000
2,50 mg (n)	14	0	14	**0,001**
3,00 mg (n)	1	0	1	1,000
5,00 mg (n)	6	0	6	0,149
10,0 mg (n)	1	0	1	1,000
Nebivolol 5mg (n)	3	0	3	0,538
Ca-antagonists (n)	7	1	6	0,395
Ace-inhibitor (n)	14	5	9	0,728
A2-RA, ARB's (n)	3	1	2	1,000
Anti-coagulants, -platelets, -aggregants (n)	37	11	26	0,316
Statins (n)	35	12	23	0,538
Fibrates (n)	1	0	1	0,684
Nitrates (n)	6	0	6	0,149
Anti-arrhythmic (n)	1	0	1	1,000
Thyroxin (+) (n)	1	0	1	1,000
Alfa1-blockers (n)	1	1	0	0,316
SSRI's (n)	1	0	1	1,000
Duration program (days)	56 (100)	56 (100)	54,5 (82)	0,653
Duration program (w)	7 (12)	7 (12)	7 (10)	0,841
Sessions (n)	21 (37)	21 (37)	20 (30)	0,841
PCI/PTCA (n)	30	11	19	0,393
CABG (n)	5	2	3	0,643
Endo-ACAB (n)	4	0	4	0,287
Endo-CABG (n)	1	0	6	1,000
FM (kg)	21,70 (36)	20,25 (12)	22 (36)	0,865
FM (%)	25,77 (32,9)	25,78 (16,1)	25,72 (32,9)	0,963
FFM (kg)	58,05 (36)	59,30 (33)	56,05 (36)	0,312
FFM (%)	74,23 (32,9)	74,22 (16,1)	74,28 (32,9)	0,963
VO2/kg peak	21,25 (18)	24,10 (12)	19,40 (18)	**0,030**
VO2 peak	1699,65 (1578)	1928,61 (1078)	1528,92 (1578)	**0,016**
METs	6,07 (5,2)	6,89 (3,4)	5,54 (5,2)	**0,030**
Watt peak	142 (156)	153 (109)	133 (156)	**0,025**

Watt/kg peak	1,74 (1,9)	2,01 (1,1)	1,57 (1,9)	**0,021**
RERpeak	1,25 (0,69)	1,30 (0,19)	1,24 (0,69)	0,065

Appendix 7: Subject characteristics PCI/CABG cohort at baseline:
Data are expressed as the median (range), Abbrevations: A2-RA: A2 -receptor antagonists, ARB's: Angiotensin 2 receptor blockers, SSRI's: Selective serotonin re-uptake inhibitors, (w): (weeks), PCI: Percutaneous coronary intervention, PTCA: Percutaneous transluminal coronary angioplasty, CABG: Coronary artery bypass graft, Endo-ACAB: Endoscopic atraumatic coronary artery bypass, Endo-CABG: Endoscopic coronary artery bypass graft, FM: Adipose tissue mass, FFM: Fat-free mass, RER: Respiratory exchange ratio = RQ: Respiratory quotiënt.
Statistical significance (Sign.) was set at p < 0,05

Appendix 7: Subject characteristics obesity cohort at baseline

Subject characteristics at baseline				P-value
	Total (n=221)	**No Bèta (n=175)**	**Bèta (n=46)**	
Age (years)	51 (63)	50 (63)	55 (56)	**0,003**
Sex (n female)	152	121	31	0,859
Weight	98,70 (156,8)	98,20 (156,8)	99,40 (92,7)	0,772
Length	1,69 (0,55)	1,68 (0,55)	1,69 (0,37)	0,551
BMI	35,00 (32)	34,70 (32)	35,90 (25)	0,344
Bisoprolol (n)	30	0	30	**0,000**
1,25 mg (n)	1	0	1	0,208
2,50 mg (n)	4	0	4	**0,002**
5,00 mg (n)	12	0	12	**0,000**
10,0 mg (n)	13	0	13	**0,000**
Nebivolol (n)	7	0	7	**0,000**
2,50 mg (n)	1	0	1	0,208
6,00 mg (n)	6	0	6	**0,007**
Metropolol (n)	4	0	4	**0,002**
50 mg (n)	1	0	1	0,208
100 mg (n)	2	0	2	**0,043**
200 mg (n)	1	0	1	0,208
Celiprolol (200 mg)	1	0	1	0,208
Propanolol (n)	5	0	5	**0,000**
40 mg (n)	1	0	1	0,208
80 mg (n)	4	0	4	0,002
Duration program (m)	6 (12)	5(12)	6 (8)	0,784
Duration program (w)	24 (50)	24 (50)	24 (34)	0,784
Sessions (n)	72 (150)	63 (150)	72 (102)	0,784

Appendix 8: Subject characteristics obesity cohort at baseline :
Data are expressed as the median (range), Abbrevations: (w): (weeks), (m): (months), BMI: Body mass index. Statistical Significance (Sign.) was set at p < 0,05.

Appendix 8: Subject characteristics obesity cohort baseline; BMI ≤ 35

	Subject characteristics at baseline		P-value
	No bèta (n=91)	**Bèta (n=20)**	
Age (years)	52 (57)	57 (50)	0,061
Sex (n female)	68	16	0,554
Weight	87,90 (67,2)	82,70 (40,9)	0,272
Length	1,67 (0,44)	1,64 (0,27)	0,292
BMI	31,70 (11)	32,30 (11)	0,959
Bisoprolol (n)	0	15	**0,000**
1,25 mg (n)	0	1	0,174
2,50 mg (n)	0	2	**0,029**
5,00 mg (n)	0	5	**0,001**
10,0 mg (n)	0	7	**0,000**
Nebivolol 5mg (n)	0	1	0,174
Metropolol 100 mg (n)	0	2	**0,029**
Celiprolol 200 mg (n)	0	1	0,174
Propanolol 80 mg (n)	0	1	0,174
Duration program (m)	6 (11)	5 (4)	0,415
Duration program (w)	25 (46)	22 (17)	0,415
Sessions (n)	75 (137)	65 (51)	0,415

Appendix 9: Subject characteristics obesity cohort baseline; BMI ≤ 35:
Data are expressed as the median (range), Abbrevations: (w): (weeks), (m): (months), BMI: Body mass index. Statistical Significance (Sign.) was set at p < 0,05.

Appendix 9: Subject characteristics obesity cohort baseline; BMI > 35

	Subject characteristics at baseline		P-value
	No bèta (n=84)	**bèta (n=26)**	
Age (years)	50 (62)	54 (47)	**0,029**
Sex (n female)	52	16	0,498
Weight	112,90 (129,5)	114,00 (70,7)	0,983
Length	1,70 (0,55)	1,70 (0,33)	0,944
BMI	38,80 (23)	39,50 (13)	0,983
Bisoprolol (n)	0	15	**0,000**
2,50 mg (n)	0	2	0,054
5,00 mg (n)	0	7	**0,001**
10,0 mg (n)	0	6	**0,001**
Nebivolol (n)	0	6	**0,003**
2,50 mg (n)	0	1	0,236
5,00 mg (n)	0	5	**0,040**
Metropolol (n)	0	2	0,054
50 mg (n)	0	1	0,236
200 mg (n)	0	1	0,236
Propanolol (n)	0	4	0,003
40 mg (n)	0	1	0,236
80 mg (n)	0	3	**0,012**
Duration program (m)	6 (12)	6 (4)	0,885
Duration program (w)	24 (50)	24 (15)	0,885
Sessions (n)	72 (150)	72 (46)	0,885

Appendix 10: Subject characteristics obesity cohort baseline; BMI > 35:
Data are expressed as the median (range), Abbrevations: (w): (weeks), (m): (months), BMI: Body mass index. Statistical Significance (Sign.) was set at p < 0,05.

Appendix 10: Subject characteristics obesity cohort baseline > AND < 35

Subject characteristics at baseline			P-value
	BMI ≤35 (n=111)	**BMI > 35 (n=110)**	
Age (years)	53 (57)	51 (62)	0,153
Sex (n female)	84	68	**0,009**
Weight	87,40 (67,2)	113,40 (129,5)	**0,000**
Length	1,66 (0,45)	1,69 (0,55)	**0,018**
BMI	31,80 (11)	38,80 (23)	**0,000**
Bèta-blockers (n)	20	26	0,407
Bisoprolol (n)	15	15	1,000
1,25 mg (n)	1	0	1,000
2,50 mg (n)	2	2	1,000
5,00 mg (n)	5	7	0,768
10,0 mg (n)	7	6	0,835
Nebivolol (n)	1	6	0,119
2,50 mg (n)	0	1	1,000
5,00 mg (n)	1	5	0,369
Metropolol (n)	2	2	1,000
50 mg (n)	0	1	1,000
100 mg (n)	2	0	0,498
200 mg (n)	0	1	1,000
Celiprolol (200 mg)	1	0	1,000
Propanolol (n)	1	4	0,369
40 mg (n)	0	1	1,000
80 mg (n)	1	3	0,622
Duration program (m)	6 (11)	6 (11)	0,579
Duration program (w)	24 (46)	24 (50)	0,579
Sessions (n)	72 (137)	72 (150)	0,579

Appendix 11: Subject characteristics obesity cohort baseline > and < 35:
Data are expressed as the median (range), Abbrevations: (w): (weeks), (m): (months), BMI: Body mass index. Statistical Significance (Sign.) was set at p < 0,05.

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Richting: **master in de revalidatiewetenschappen en de kinesitherapie-revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen**
Jaar: **2016**

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