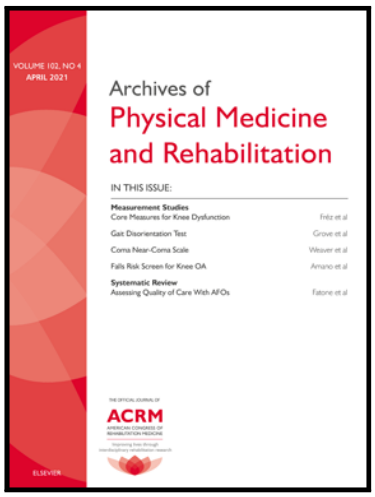

Cost-effectiveness of a cardiac rehabilitation program specifically designed for patients with obesity within the OPTICARE XL randomized controlled trial

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Cost-effectiveness of a cardiac rehabilitation program specifically designed for patients with obesity within the OPTICARE XL randomized controlled trial

Running head

Costs and health benefits of OPTICARE XL

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Conflicts of interest

Conflicts of interest: none declared.

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STRUCTURED ABSTRACT

Objective To assess the cost-effectiveness of a cardiac rehabilitation (CR) program specifically designed for cardiac patients with obesity versus standard CR.

Design Cost-effectiveness analysis based on observations in a randomized controlled clinical trial.

Setting Three regional CR centres in the Netherlands.

Participants Cardiac patients (N=201) with obesity (BMI≥30 kg/m^2) referred to CR.

Interventions Participants were randomised to a CR program specifically designed for patients with obesity (OPTICARE XL; N=102) or standard CR. OPTICARE XL included aerobic and strength exercise and behavioural coaching on diet and physical activity during 12 weeks, followed by a 9 month after-care program with 'booster' educational sessions. Standard CR consisted of a 6 to 12-week aerobic exercise program, supplemented with cardiovascular lifestyle education.

Main outcome measures An economic evaluation, with an 18-month time horizon, in terms of quality-adjusted life years (QALYs) and costs from the societal perspective was performed. Costs were reported in 2020 Euros, discounted at a 4% annual rate, and health effects were discounted at a 1.5% annual rate.

Results OPTICARE XL CR and standard CR resulted in comparable health gain per patient (0.958 versus 0.965 QALYs, respectively; p=0.96). Overall, OPTICARE XL CR saved costs (-€4,542) compared to the standard CR group. The direct costs for OPTICARE XL CR were higher than for standard CR (€10,712 vs. €9,951), whereas indirect costs were lower (€51,789 vs. €57,092), but these differences were not significant.

Conclusions This economic evaluation showed no differences between OPTICARE XL CR and standard CR in health effects and costs in cardiac patients with obesity.

Trial registration Prospectively registered in the International Clinical Trial Registry Platform (ICTRP), https://trialsearch.who.int/. Main ID: NTR6181.

Key words

Cardiac rehabilitation, cost-effectiveness analysis, obesity

List of abbreviations

AF = atrial fibrillation

CAD = coronary artery disease

CHEERS = consolidated health economic evaluation reporting standard

CR = cardiac rehabilitation

CVD = cardiovascular disease

EQ-5D-5L = EuroQol 5 Dimensions with 5 levels questionnaire

ESC = European Society of Cardiology

ICER = incremental cost effectiveness ratio

iMCQ = iMTA Medical Consumption Questionnaire

iPCQ = iMTA Productivity Costs Questionnaire

QALY = quality adjusted life year

INTRODUCTION

The prevalence of cardiac diseases and obesity are predicted to rise in the future in Europe.(1) The EUROASPIRE V survey found that 38% of patients with cardiovascular disease (CVD) is affected by obesity.(2) Obesity is a worldwide chronic disease (3) with a predicted prevalence in Europe ranging from 13% to 43% by 2025.(4) Not only is obesity a major risk factor for coronary artery disease (CAD), it also substantially increases the risk of atrial fibrillation (AF).(5) Moreover, obesity is a significant driver of healthcare expenditures.(6, 7). Based on health economic models, 2.1% - 4.7% of total health care costs and 2.8% of total hospital costs are attributable to overweight and obesity in Europe.(6)

According to guidelines, patients with cardiac diseases should be referred to cardiac rehabilitation (CR) for secondary prevention and management of cardiovascular risk factors.(8, 9) CR is a multidisciplinary treatment combining exercise training and education sessions to reduce risk of a recurrent cardiovascular event, reduce mortality, and improve quality of life.(8, 9) Alarmingly, the majority of patients with obesity start CR with a poorer cardiovascular risk profile, including a higher prevalence of hypertension, hyperlipidaemia, and a less physically active and more sedentary lifestyle than patients without obesity.(10, 11) Furthermore, patients with obesity only achieve small improvements in fitness level during CR compared to patients with normal weight, and weight loss results are unsatisfactory.(12, 13)

These observations suggest that cardiac patients with obesity may benefit more from a specific CR program to help them to adopt and sustain a healthy and active lifestyle. Such a program should include a behavioural weight loss intervention, an exercise program suitable

for patients with obesity consisting of a combination of aerobic exercise and muscle strength training, and prolonged coaching.(14, 15) Against this background, we developed a peer group CR program, OPTICARE XL, focussing on self-management and behavioural changes targeting CAD and AF patients with obesity. With help of this program we aimed to improve CR outcomes for patients with obesity, thereby decreasing healthcare costs for society.

A Cochrane review on exercised-based CR for persons with cardiac diseases indicated that CR can be a potential cost-effective use of resources in terms of health gain when compared to usual care, defined as standard medical care such as drug therapy but without any form of structural exercise training or advice.(16) Furthermore, a meta-analysis examining the cost-effectiveness of CR in patients with CAD indicated that comprehensive CR, defined as CR that includes exercise therapy, patient education, and psychological or lifestyle guidance, is generally considered cost-effective compared to usual care.(17) Whilst these papers find CR to have the potential to be cost-effective, these studies compared CR to usual care and not to peer group CR programs designed for patients with obesity.

We recently completed a randomised controlled clinical trial to study the effects of OPTICARE XL CR compared with standard CR in obese patients with CAD or AF on a broad range of clinically relevant endpoints. Compared with standard CR, some beneficial effects were observed on physical and psychosocial outcomes in the active CR period, but these did not last during post CR follow-up.(18, 19) The current paper describes the results of a cost-effectiveness analysis based on these trial data, which can contribute to the positioning of OPTICARE XL CR in the target group.

METHODS

Study design

OPTICARE XL is a multicentre randomised controlled trial performed in patients with documented CAD or nonvalvular AF, and who had a body mass index (BMI) ≥30 kg/m^2 at randomization. In three regional CR centres in The Netherlands, eligible patients were randomized to OPTICARE XL CR or standard CR, and subsequently followed-up until 18 months after the start of CR. The trial protocol was approved by the Medical Ethics Committee of Erasmus MC, University Medical Centre Rotterdam, The Netherlands (MEC-2016-622). All participants provided written informed consent.

CR program

The OPTICARE XL CR peer group program was specifically designed for cardiac patients with obesity, focussing on self-management and behavioural change. The program was based on the multidisciplinary CR guidelines of the European Society of Cardiology (ESC), and on the Dutch dietary guidelines on food intake and food choices and on the Dutch Physical Activity Guidelines.(20-23) Patients randomised to OPTICARE XL CR followed a one-year program in groups of 6 to 8 patients. During the first three months, patients participated in exercise training, comprising a combination of aerobic and muscle strength exercises two times per week. Additionally, they received two peer group coaching modules to create awareness about a healthy diet (12 sessions), and about an active and less sedentary lifestyle (4 sessions). General education on cardiovascular risk factors and facultative modules (e.g., on smoking cessation) were also offered to patients allocated to OPTICARE XL CR. During the next 9 months, patients received six educational 'booster' sessions on diet and an active lifestyle. A more extensive description of OPTICARE XL CR can be found elsewhere.(18)

Patients randomised to standard CR followed a program in line with the usual ESC CR guidelines, which does not differentiate between patients with and without obesity.(8, 22) For a duration of 6-12 weeks, patients participated in group-based exercise sessions two times per week, which only consisted of aerobic exercises. Furthermore, general educational sessions on cardiovascular risk factors and facultative modules on for example smoking cessation were provided. There was no after-care program.

Study design: economic model

This is a trial-based economic evaluation to assess the cost-effectiveness of OPTICARE XL CR versus standard CR in terms of quality adjusted life years (QALYs) and costs from a societal perspective in the Dutch healthcare setting. An economic evaluation relates the incremental costs of an alternative intervention to the incremental clinical health effect of this alternative intervention, which is expressed as the incremental cost effectiveness ratio (ICER). The measure of health is a generic measure of health gain ('utility'), in this study expressed in terms of QALYs, and allows for the comparability of these alternative interventions expressed in terms of costs per QALY gained.(24) The incremental costs are compared to a threshold that society is willing to pay per additional QALY gained due to the intervention. In the Netherlands the maximum threshold is set at €80,000 per QALY gained.(25) The consolidated health economic evaluation reporting standard (CHEERS) checklist was used.(26)

Perspective and time horizon

In accordance with Dutch economic guidelines, a societal perspective was taken, which means that all costs and effects borne by society are considered, regardless of who incurs the costs or receives the potential effects.(25) Costs were discounted at a 4% annual rate, and

health effects were discounted at a 1.5% annual rate.(27) We used an 18-month time horizon (equal to the follow-up period of the trial) because we expected that all differences in costs and effects would appear within that period.(18, 27)

Societal costs

Given the societal perspective, costs included in the analysis were health care costs (costs directly related to the intervention, e.g. healthcare staff costs to provide the intervention), non-health care costs (indirect costs in other sectors due to e.g. productivity loss at work), and costs incurred by patient and family (e.g. informal care provided by family or friends).(27) We did not include healthcare costs incurred due to a longer life since we expected no difference in mortality rate between the two groups.

To quantify direct and indirect costs incurred by the patient, the iMTA Medical Consumption Questionnaire (iMCQ) (28) and the iMTA Productivity Costs Questionnaire (iPCQ) were used.(29) The 18-item iMCQ measures the medical consumption of a patient, such as the number of visits to healthcare professionals.(28) Costs are calculated by multiplying the resource use with the unit costs. The iPCQ measures and values productivity costs, such as costs due to absence from work (absenteeism) or being less productive at work due to illness (presenteeism), and loss of productivity at unpaid work.(29) Start and end dates were recorded for absence from work due to illness, and for reduced productivity at work due to illness. Productivity costs were calculated by multiplying the days absent from work with a cost price. Long-term productivity costs were calculated using the friction cost method (29), which assumes that all persons that are absent from work due to illness are replaceable. Therefore, productivity costs are incurred over the time it takes to replace the person absent from work; in the Netherlands, this so-called friction period is taken to be 85 days.(27, 30, 31)

Intervention-related costs were based on the resources used (e.g. number of health professionals involved, physiotherapy sessions, and educational sessions) and internal pricing. When relevant, the costs were based on either the Dutch Costing Manual (2015) or literature search (Table 1).(25)

Patient and productivity costs collected using the iMCQ and iPCQ were measured at baseline and each follow-up moment. For patients allocated to OPTICARE XL CR, follow-up moments were set at T3M (M = months; directly after completion of the first part of OPTICARE XL CR), T12M (directly after completion of the second part of OPTICARE XL CR), and T18M (6 months after completion of OPTICARE XL CR). For patients allocated to standard CR, follow-up moments were set at T3M (directly after completion of standard CR), T9M (6 months after completion of standard CR), and T18M (18 months after the start of standard CR). Total costs were calculated by combining the recall periods of the questionnaires, which was 3 months for the iMCQ and 4 weeks for the iPCQ. Costs are reported in 2020 Euros and corrected using the consumer price index when necessary.

Health outcomes

The health effects were measured using the generic EuroQol 5 Dimensions with 5 levels questionnaire (EQ-5D-5L). The EQ-5D-5L is a validated instrument providing a single generic measure of health commonly used in clinical and economic evaluations.(27, 32) The EQ-5D-5L results can be converted into a single "health utility" score, where 0 equals death and 1.0 equals perfect health.(33) The health utility score is calculated using the Dutch country value set.(34) The utility scores, measured at each follow-up moment, are combined to estimate the QALYs per patient. The QALY is a measure to estimate health as a function of

life-years and the quality of life lived in those years.(35) The EQ-5D-5L was measured at baseline and each follow-up moment. The total number of QALY's was calculated by combining health utility scores with follow-up durations.

Statistical analysis

All patients that had at least one measurement, either at baseline or follow-up, were included in the analysis. Since we had complete data for 71.2% of our values, we performed multiple imputation, based on the assumption of data missing at random.(36) We created 5 imputed data sets to preserve the existing uncertainty in the original data set. Missing data for costs and health effects were estimated using baseline characteristics (sex, age, BMI), reason for referral to CR, marital status, educational level, work status, and cardiac risk factors, EQ-5D-5L, iMCQ, and the iPCQ data collected. Total costs and health effects were then estimated using that complete dataset.

Statistical differences in mean costs and health effects between the two interventions were examined using Students' t-test. To describe the effects of sampling uncertainty for the estimated costs and health effects univariate linear regression analysis was applied using the imputed dataset.

RESULTS

Patients

A total of 102 patients were randomized to OPTICARE XL CR and 99 to standard CR between February 2017 and January 2019. Measurements were completed in July 2020. Most of the patients were male (73%), with a mean age of 59 years and a BMI of 34 kg/m^2 (Table

2). The majority of the patients (66%) were referred to CR for CAD. Approximately half of the patients had a family history of CVD and 28% suffered from diabetes.

Health effects and incremental costs

The patients of both OPTICARE XL CR and standard CR showed very similar health outcomes with cumulative QALYs per patient of 0.958 versus 0.965, respectively (p=0.96).

The mean total direct and indirect costs per patient and the mean incremental costs per QALY gained are described in Table 3. Mean intervention-related costs in patients randomized to OPTICARE XL CR were higher than in patients randomized to standard CR (€3,986 versus €2,784 per patient, respectively) but mean medical-related costs and indirect costs were lower. Altogether, mean total costs in patients randomized to OPTICARE XL CR were €4,542 lower than in standard CR, but this difference was not statistically significant. Overall, the incremental costs per QALY were € 608k. This can be interpreted as costs saved for the OPTICARE XL CR program per lost QALY, in which the 0.0075 QALY loss is a loss of almost three days for the OPTICARE XL CR group, thus a limited loss given the costs-savings.

Breakdown of costs per follow-up moment

A detailed overview of the costs per category and follow-up moment is presented in Table 4 (direct costs) and Table 5 (indirect costs). We did not find any significant differences in the separate cost categories.

DISCUSSION

Our economic evaluation based on data obtained in a randomised trial found non-significant cost savings and no additional health gains for the OPTICARE XL CR program compared to standard CR in cardiac patients with obesity. To our knowledge, this is the first economic evaluation performed in a dedicated CR program designed for patients with obesity.

In our study, we found non-significant cost-savings and a small QALY loss, which resulted in an ICER of €608k which can be interpreted as costs saved per lost QALY. However, the relatively large confidence intervals found regarding the mean total direct and indirect costs suggest cautious interpretation of these results. Since the ICER is above the highest willingness-to-pay threshold of €80,000, it could suggest that the small QALY loss is acceptable given the amount of costs saved. Re-designing the OPTICARE XL program may have the potential to make the OPTICARE XL CR program cost-effective compared to standard CR when (even more) focus is placed on improving the health of the patients involved in the trial.

In our previously published paper on the effectiveness of the OPTICARE XL CR program on parameters of a heart-healthy lifestyle, we concluded that the program did not result in persistent larger improvements than standard CR.(19) In line with these outcomes, additional health gains (expressed in QALY's) were also not found in the current analysis for patients participating in the new OPTICARE XL CR. Relevant short-term improvements were observed in weight loss and physical activity in our previously published paper, however these were observed only at three months and not thereafter. Therefore, we advised to re-design the after-care phase of the OPTICARE XL CR program, such that improvements in weight loss and physical activity can be expanded.(19) The use of digital platforms as well as increasing the frequency of sessions during this part of the program were suggested as

possible adaptations. Additional health benefits might be observed when OPTICARE XL CR is redesigned. If successful, then future cost-effectiveness analyses should extrapolate these long-term health benefits because we may then assume that there will be differences in long term health between the two CR programs (as opposed to the assumption in the current analysis that there are no differences in long term health or costs thus no extrapolation of data was conducted).

We hypothesized that standard CR would be associated with higher medical-related costs as well as higher indirect costs compared to the OPTICARE XL CR group. This was expected because the standard CR patients would receive less intensive care and perhaps therefore seek more medical care beyond the scope of the trial. While these costs were indeed lower for the OPTICARE XL program, we did not observe a significant difference in costs between both strategies. For example, we observed minimal differences in costs related to physiotherapy and visits to the dietician, while the OPTICARE XL CR program is focused on such aspects. Therefore, in the redesign of the program, even more focus should be placed on that such that the participants do not need to seek such medical care beyond the program and therefore save costs. Another possibility why we did not observe significant differences in costs might be explained by the design of the study, namely an intensive randomized controlled trial with a follow-up period of 18 months, focussing on a CR program especially designed for patients with obesity. Therefore, we cannot rule out that we selected motivated patients willing to work on their health, thereby missing out on the patients with obesity in need of the most intensive care. The program is designed for patients with obesity, and while this program is not significantly cheaper and minimal differences are seen in health gain, it nevertheless may be a good alternative for exactly these patients that are less motivated to change their lifestyle.

A strength of this economic evaluation is that it focuses on CR for persons with a major comorbidity, obesity. Edwards *et al.* notes that while there is evidence that supports the cost-effectiveness of exercise-based CR for CVD patients (e.g. hospital-based CR vs standard care or no CR, or exercise-based CR in a rehabilitation centre vs conventional care without exercise) none considered comorbidities as a factor.(37) Since it is known that obesity is a significant driver of healthcare expenditures (6, 7), this is of great importance. Secondly, in line with economic evaluations on CR, we performed a trial-based economic evaluation and present the actual impact of CR therapy measures on costs and effects seen in the trial rather than based on a Markov model. Values used in Markov models are derived from secondary data sources, which may therefore limit the interpretability and relevance of the results.(27) Thirdly, we provide a detailed overview of the costs persons with obesity incur during a CR program. These costs can be used as input for future economic evaluations.

Study limitations

This study also has some limitations. Not all questionnaires were filled out completely, leading to selection bias and missing data. To reduce bias due to missing data we used multiple imputation to complete the dataset, which is the preferred method according to the Dutch economic guidelines.(27) Furthermore, while the OPTICARE XL CR trial was conducted in three locations in the Netherlands, we cannot generalize the results to other healthcare settings beyond the Netherlands.

CONCLUSION

This economic evaluation showed that the OPTICARE XL CR program versus standard CR in patients with obesity has non-significant cost savings and no additional health gain. The

OPTICARE XL CR program is innovative with regard to focussing on CR for patients with obesity, an area that has been underexplored and therefore worthy of more attention given population trends. However, more research is needed to understand why the new CR program does not yet improve health outcomes, and therefore a re-design of the CR program is advised.

REFERENCES

1. Timmis A, Townsend N, Gale CP, Torbica A, Lettino M, Petersen SE, et al. European Society of Cardiology: cardiovascular disease statistics 2019. European heart journal. 2020;41(1):12-85.

2. Kotseva K, De Backer G, De Bacquer D, Rydén L, Hoes A, Grobbee D, et al. Lifestyle and impact on cardiovascular risk factor control in coronary patients across 27 countries: Results from the European Society of Cardiology ESC-EORP EUROASPIRE V registry. European journal of preventive cardiology. 2019;26(8):824-35.

3. World Health Organization. Obesity and overweight [internet] cited 2020 Jul 15 [Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight].

4. Pineda E, Sanchez-Romero LM, Brown M, Jaccard A, Jewell J, Galea G, et al. Forecasting future trends in obesity across Europe: the value of improving surveillance. Obesity facts. 2018;11(5):360-71.

5. Wanahita N, Messerli FH, Bangalore S, Gami AS, Somers VK, Steinberg JS. Atrial fibrillation and obesity—results of a meta-analysis. American heart journal. 2008;155(2):310-5.

6. von Lengerke T, Krauth C. Economic costs of adult obesity: a review of recent European studies with a focus on subgroup-specific costs. Maturitas. 2011;69(3):220-9.

7. Withrow D, Alter DA. The economic burden of obesity worldwide: a systematic review of the direct costs of obesity. Obesity reviews. 2011;12(2):131-41.

8. Nederlandse Vereninging voor Cardiologie. Revalidatiecommissie NVVC/NHS en projectgroep PAAHR. Multidisciplinaire Richtlijn Hartrevalidatie. 2011.

9. Piepoli MF, Corra U, Benzer W, Bjarnason-Wehrens B, Dendale P, Gaita D, et al. Secondary prevention through cardiac rehabilitation: from knowledge to implementation. A

position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation. European Journal of Cardiovascular Prevention & Rehabilitation. 2010;17(1):1-17.

10. NCD Risk Factor Collaboration. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19· 2 million participants. The lancet. 2016;387(10026):1377-96.

11. den Uijl I, Ter Hoeve N, Sunamura M, Lenzen MJ, Braakhuis HE, Stam HJ, et al. Physical Activity and Sedentary Behavior in Cardiac Rehabilitation: Does Body Mass Index Matter? Physical Therapy. 2021.

12. Gunstad J, Luyster F, Hughes J, Waechter D, Rosneck J, Josephson R. The effects of obesity on functional work capacity and quality of life in phase II cardiac rehabilitation. Preventive cardiology. 2007;10(2):64-7.

13. Martin BJ, Aggarwal SG, Stone JA, Hauer T, Austford LD, Knudtson M, et al. Obesity Negatively Impacts Aerobic Capacity Improvements Both Acutely and 1-Year Following Cardiac Rehabilitation. Obesity. 2012;20(12):2377-83.

14. Ho SS, Dhaliwal SS, Hills AP, Pal S. The effect of 12 weeks of aerobic, resistance or combination exercise training on cardiovascular risk factors in the overweight and obese in a randomized trial. BMC public health. 2012;12(1):1-10.

15. Schjerve IE, Tyldum GA, Tjønna AE, Stølen T, Loennechen JP, Hansen HE, et al. Both aerobic endurance and strength training programmes improve cardiovascular health in obese adults. Clinical science. 2008;115(9):283-93.

16. Anderson L, Thompson DR, Oldridge N, Zwisler AD, Rees K, Martin N, et al. Exercise-based cardiac rehabilitation for coronary heart disease. Cochrane Database of Systematic Reviews. 2016(1).

17. Takura T, Ebata-Kogure N, Goto Y, Kohzuki M, Nagayama M, Oikawa K, et al. Cost-effectiveness of cardiac rehabilitation in patients with coronary artery disease: a meta-analysis. Cardiology research and practice. 2019;2019.

18. den Uijl I, Ter Hoeve N, Sunamura M, Stam HJ, Boersma E, Lenzen MJ, et al. Cardiac rehabilitation designed for patients with obesity: OPTICARE XL RCT results on health-related quality of life and psychosocial well-being. Disability and Rehabilitation. 2022:1-10.

19. den Uijl I, van den Berg-Emons RJ, Sunamura M, Lenzen MJ, Stam HJ, Boersma E, et al. Effects of a dedicated cardiac rehabilitation program for patients with obesity on body weight, physical activity, sedentary behaviour and physical fitness: the OPTICARE XL randomized controlled trial [Submitted]. 2022.

20. Health Council of the Netherlands. Guidelines for a healthy diet 2015 (Richtijnlijk Goede Voeding 2015). The Hague: Health Council of the Netherlands (Gezondheidsraad), 2015.

21. Health Council of the Netherlands. Advies Beweegrichtlijnen 2017, 2017.

22. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. Guidelines: Editor's choice: 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). European heart journal. 2016;37(29):2315.

23. Weggemans RM, Backx FJ, Borghouts L, Chinapaw M, Hopman MT, Koster A, et al. The 2017 Dutch physical activity guidelines. International Journal of Behavioral Nutrition and Physical Activity. 2018;15(1):1-12.

24. Drummond MF SM, Claxton K, Stoddart GL, Torrance GW. Introduction to Economic Evaluation. 4th ed. Methods for the Economic Evaluation of Health Care Programmes. Oxford: Oxford Universiy Press; 2015.

25. Nederlands Zorginstituut. Kosteneffectiviteit in de praktijk (Cost-effectiveness analysis in practice). Diemen; 2015.

26. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated health economic evaluation reporting standards (CHEERS)—explanation and elaboration: a report of the ISPOR health economic evaluation publication guidelines good reporting practices task force. Value in health. 2013;16(2):231-50.

27. Nederlands Zorginstituut. Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg. Diemen, 2016.

28. Bouwmans C, Hakkaart-Van Roijen L, Koopmanschap M, Krol M, Severens S, Brouwer W. iMTA Medical Consumption Questionnaire Handleiding. Hoboken: Institute for Medical Technology Assessment Erasmus Universiteit Rotterdam. 2013.

29. Bouwmans C, Krol M, Severens H, Koopmanschap M, Brouwer W, Hakkaart-van Roijen L. The iMTA productivity cost questionnaire: a standardized instrument for measuring and valuing health-related productivity losses. Value in health. 2015;18(6):753-8.

30. Hakkaart-van Roijen L, Van der Linden N, Bouwmans C, Kanters T, Tan SS. Kostenhandleiding. Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg In opdracht van Zorginstituut Nederland Geactualiseerde versie. 2015.

31. Koopmanschap MA, Rutten FF, van Ineveld BM, Van Roijen L. The friction cost method for measuring indirect costs of disease. Journal of health economics. 1995;14(2):171-89.

32. Janssen M, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Quality of Life Research. 2013;22(7):1717-27.

33. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of life research. 2011;20(10):1727-36.

34. Versteegh M. M Vermeulen K, MAA Evers S, et al. Dutch tariff for the five-level version of EQ-5D Value Health. 2016;19:343-52.

35. National Institue for Health and Care Excellence. Glossary [Internet] [cited 2020 Apr 24] [Available from: https://www.nice.org.uk/Glossary].

36. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. Bmj. 2009;338.

37. Edwards K, Jones N, Newton J, Foster C, Judge A, Jackson K, et al. The cost-effectiveness of exercise-based cardiac rehabilitation: a systematic review of the characteristics and methodological quality of published literature. Health economics review. 2017;7(1):1-23.

TABLES

Table 1 Unit costs and resource utilisation (Euros 2020).

Resource use	**Unit cost (€)**	**Reference**
Direct costs		

Intervention-related costs		
- OPTICARE XL CR	3986	Internal reference pricing
- Standard CR	2785	Internal reference pricing
Medical related costs		
General practitioner	36	(28)
Social worker	70	(28)
Physiotherapy	36	(28)
Ergotherapy	36	(28)
Logotherapy	32	(28)
Dietician	63[1]	(36)
Homeopathy	1st consult: 75 2nd consult: 55[1]	(37)
Psychologist	102	(28)
Occupational practitioner	36[2]	(28)
Ambulance ride	557	(28)
Emergency room	280	(28)
Hospitalization		
- Cardiology ward	515[3]	(28)
- Surgical ward	438	(28)
- Neurology ward	427	(28)
- Other	515[3]	(28)
Outpatient clinic visit		
- Cardiology	98[4]	(28)
- General surgery	79	(28)

- Neurology	107	(28)
- Other outpatient clinic	98[4]	(28)
Indirect costs		
Home care		
- Domestic help	22	(28)
- Nursing care	79	(28)
Informal care		
- Domestic help	15	(28)
- Personal care	15	(28)
- Practical help	15	(28)
Productivity costs		
- Short-term productivity costs (<4 weeks)	39[5]	(28)
- Long-term productivity costs (>4 weeks)	39[5]	(28)
- Presenteeism	39[5]	(28)
- Unpaid work	15	(28)

[1]These are the minimum costs per resource use provided on the websites, therefore a potential underestimation of the true costs, [2]We assumed the costs of the occupational practitioner to equal a consult with a general practitioner since no tariffs could be found in the literature,[3]We assume that the cardiology ward and 'other' wards (e.g. internal medicine or ophthalmology/eye ward) have a unit price equal to the unit cost of a general ward since no unit prices are provided in the Dutch cost manual, [4]We assume that the unit price of the

cardiology outpatient clinic and 'other' outpatient clinic visits (e.g. internal medicine) are equal to the unit cost of a general outpatient clinic visit since no unit prices are provided in the Dutch cost manual, [5]*The cost of productivity is weighted according to the male to female ratio in the study population (73% vs 27%).*

Table 2 Baseline characteristics of study population.

	OPTICARE XL CR (n=102)	**Standard CR (n=99)**
Males, n (%)	68 (66.7)	78 (78.8)
Age (years)[1]	59.0 ± 10.0	59.2 ± 8.8
BMI (kg/m^2)[2]	34.4 ± 4.7	34.1 ± 4.6
Referred to CR for, n (%)		
- CAD	62 (60.8)	71 (71.7)
- AF with ablation	7 (6.9)	4 (4.0)
- AF without ablation	33 (32.4)	24 (24.2)
Marital status, n (%)		
- Partnered	71 (74.7)	69 (77.5)
- Unpartnered	24 (25.3)	20 (22.5)
Missing	*7*	*10*
Educational level, n (%)		
- Low	8 (8.5)	5 (5.7)
- Intermediate	58 (61.7)	65 (73.9)
- High	28 (29.8)	18 (20.5)
Missing	*8*	*11*
Work status, n (%)		
- Employed	50 (53.2)	56 (66.7)
- Unemployed	44 (46.8)	28 (33.3)
Missing	*8*	*15*
Risk factors, n (%)		

- Family history of CVD	48 (47.1)	50 (50.5)
- Diabetes	29 (28.4)	28 (28.3)
- Hypertension	57 (55.9)	57 (57.6)
- Dyslipidaemia	33 (32.4)	49 (49.5)
- Smoking before CR	33 (32.4)	25 (25.3)

CR = cardiac rehabilitation; CAD = coronary artery disease; AF = atrial fibrillation; CVD = cardiovascular disease

[1] *Normally distributed: mean ± SD*

[2] *Not normally distributed: mean ± IQR*

Table 3 Cardiac rehabilitation costs and health effects per patient for OPTICARE XL and standard CR group.

	OPTICARE XL CR	**Standard CR**	**Difference OPTICARE XL CR versus standard CR**
Mean total per patient	**€ 62.501**	**€ 67.043**	**-€ 4.542**
DIRECT COSTS			
Mean costs per patient			
Intervention-related costs	€ 3.986	€ 2.784	€ 1.202
Medical-related costs	€ 6.726	€ 7.167	-€ 441
Total	*€ 10.712*	*€ 9.951*	*€ 761*
Mean total direct costs per follow-up moment (95% CI)[1]			
T3m	€ 2.072	€ 1.846	€ 225 (-180, 631)
T12m (OPTICARE XL CR) / T9m (Standard CR)	€ 4.819	€ 3.220	€ 1598 (122, 3075)*
T18m	€ 3.922	€ 4.983	-€ 1061 (-2739, 617)
INDIRECT COSTS			
Mean costs per patient			
Home care	€ 1.020	€ 1.156	-€ 136

Informal care	€ 4.941	€ 6.484	-€ 1.543
Productivity costs - Short-term productivity costs (<4 weeks) - Long-term productivity costs (>4 weeks) - Presenteeism - Unpaid work	 € 1.288 € 41.455 € 567 € 2.518	 € 1.802 € 43.812 € 864 € 2.974	 -€ 515 -€ 2.357 -€ 296 -€ 456
Total	*€ 51.789*	*€ 57.092*	*-€ 5.303*
Mean total indirect costs per follow-up moment (95% CI)			
T3m	€ 8.888	€ 11.120	-€ 2232 (-5301, 835)
T12m (OPTICARE XL CR) / T9m (Standard CR)	€ 27.435	€ 21.577	€ 5857 (-8060, 19775)
T18m	€ 16.920	€ 29.080	-€ 11692 (-40645, 17261)
HEALTH EFFECTS			
Mean health utility per follow-up moment (95% CI)			
EQ-5D utility			
Baseline	0.72	0.70	0.02 (-0.008, 0.050)
T3m	0.72	0.70	0.02 (-0.068, 0.109)
T12m (OPTICARE XL CR) /	0.64	0.63	0.015 (-0.095, 0.124)

T9m (Standard CR)			
T18m	0.60	0.64	-0.04 (-0.164, 0.076)
Mean QALY per patient			
Mean QALYs (95% CI)	*0.321*	*0.324*	*-0.0034 (0.046, 0.039)*
T3m	0.181	0.176	0.005 (-0.017, 0.027)
T12m (OPTICARE XL CR) / T9m (Standard CR)	0.481	0.314	0.168 (0.099, 0.235)**
T18m	0.300	0.484	-0.183 (-0.267, -0.099)**
Total QALY	0.958	0.965	-0.0075
INCREMENTAL COST PER QALY			**€ 608.118 (costs saved per lost QALY)**

QALY = quality-adjusted life years; CI = confidence interval.

T3M: follow-up moment at 3 months (first follow-up moment for both groups), T9M: follow-up moment at 9 months (second follow-up moment for standard CR), T12M: follow-up moment at 12 months (second follow-up moment for OPTICARE XL CR), T18M: follow-up moment at 18 months (third follow-up moment for both groups).

Costs and health effects are discounted regarding the results per patient, but are not discounted per follow-up moment, though they are corrected for time (weighting recall period and time between follow-up).

[1]*Includes the intervention-related costs.*

**Sig <0.05, **Sig <0.00, Sig differences due to weighting.*

Table 4 *Breakdown of costs incurred during the study (direct costs).*

	OPTICARE XL				**Standard CR**				**p-value**
	Total[1]	**T3m**	**T12m**	**T18m**	**Total[1]**	**T3m**	**T9m**	**T18m**	
Direct costs									
Medical-related costs (unit cost; range)	*€ 6726*				*€ 7167*				*0.81*
General practitioner (€36; 0-540)	€ 349	€ 59	€ 57	€ 62	€ 391	€ 58	€ 64	€ 70	
Social worker (€70; 0-280)	€ 139	€ 18	€ 21	€ 30	€ 128	€ 17	€ 22	€ 23	
Physiotherapy (€36; 0-720)	€ 620	€ 76	€ 107	€ 116	€ 657	€ 99	€ 111	€ 115	
Ergotherapy (€36; 0-1269)	€ 386	€ 22	€ 74	€ 74	€ 302	€ 26	€ 40	€ 67	
Logotherapy (€32; 0-	€ 136	€ 8	€ 26	€ 26	€ 110	€ 10	€ 15	€ 24	

384)									
Dietician (€63; 0-756)	€ 314	€ 51	€ 50	€ 59	€ 366	€ 73	€ 59	€ 60	
Homeopathy (€75/55; 0-405)	€ 123	€ 7	€ 18	€ 32	€ 115	€ 20	€ 24	€ 16	
Psychologist (€102; 0-1224)	€ 494	€ 38	€ 97	€ 86	€ 420	€ 47	€ 65	€ 83	
Occupational practitioner(€36; 0-175)	€ 91	€ 24	€ 12	€ 16	€ 113	€ 29	€ 17	€ 17	
Ambulance ride (€557; 0-557)	€ 824	€ 84	€ 135	€ 174	€ 959	€ 109	€ 149	€ 189	
Emergency room (€280; 280-840)	€ 401	€ 59	€ 71	€ 67	€ 466	€ 62	€ 66	€ 93	
Hospitalization - 1st hospitalization (€515/438/427;	€ 1.146	€ 88	€ 209	€ 224	€ 1.324	€ 134	€ 215	€ 260	

438- 5665)[2]									
- 2nd hospitalization (€515/438/427; 0-2060)[2]	€ 822	€ 78	€ 143	€ 164	€ 937	€ 103	€ 142	€ 188	
Outpatient clinic visit									
- 1st visit (€98/79/107; 0 - 749)[3]	€ 465	€ 81	€ 74	€ 84	€ 478	€ 77	€ 88	€ 77	
- 2nd visit (€98/79/107; 0 - 428)[3]	€ 232	€ 25	€ 42	€ 42	€ 230	€ 37	€ 44	€ 36	
- 3rd visit (€98/79/107; 0-882)[3]	€ 185	€ 24	€ 28	€ 40	€ 171	€ 18	€ 27	€ 34	

[1]The total costs are corrected for time (weighting recall period and time between follow-up), [2]Unit costs depend on the type of ward the patient is admitted to for hospitalization (cardiology: €515, surgical: €438, neurology: €427, other: €515), [3]Unit costs depend on the type of outpatient clinic the patient visits (cardiology: €98, surgical: €79, neurology: €107, other: €98)

Table 5 *Breakdown of costs incurred during the study (indirect costs).*

	OPTICARE XL				**Standard CR**				**p-value**
	Total[1]	**T3m**	**T12m**	**T18m**	**Total[1]**	**T3m**	**T9m**	**T18m**	
Indirect costs									
Home care	*€ 1020*				*€ 1156*				*0.64*
- Domestic help (€22; 0-1287)	€ 461	€ 53	€ 79	€ 89	€ 464	€ 50	€ 87	€ 82	
- Nursing care (€79; 0-1580)	€ 559	€ 70	€ 93	€ 109	€ 692	€ 70	€ 118	€ 132	
Informal care	*€ 4941*				*€ 6484*				*0.80*
- Domestic help (€15.14; 0-15745)	€ 4.086	€ 378	€ 650	€ 914	€ 5.163	€ 647	€ 732	€ 1044	
- Personal care (€15.14; 0-394)	€ 64	€ 15	€ 13	€ 5	€ 166	€ 26	€ 23	€ 32	

- Practical help (€15.14; 0-4087)	€ 792	€ 141	€ 160	€ 89	€ 1.156	€ 192	€ 162	€ 219	
Productivity costs	*€ 45.828*				*€ 49.452*				*0.95*
- Short-term productivity costs (<4 weeks) (€39.15; 0 - 12919)	€ 1.288	€ 559	€ 116	€ 198	€ 1.802	€ 779	€ 177	€ 229	
- Long-term productivity costs 1 (€39.15; 0- 20973)[2]	€ 984	€ 148	€ 112	€ 260	€ 901	€ 175	€ 119	€ 167	
- Long-term productivity costs 2 (€39.15)[3]	€ 40.471	€ 6968	€ 7421	€ 5845	€ 42.911	€ 8579	€ 8575	€ 5878	
- Presenteeism									

- Unpaid work (€15.14; 0-9084)	€ 567 € 2.518	€ 152 € 404	€ 100 € 402	€ 60 € 472	€ 864 € 2.974	€ 212 € 390	€ 203 € 592	€ 84 € 479	

[1]The total costs are corrected for time (weighting recall period and time between follow-up), [2]Duration of absence from work is longer than 4 weeks, but shorter than the friction cost period, [3]Duration of absence from work is exceeds the friction cost period (85 days) but part of the friction cost period falls in between two follow-up moments.