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Cost–utility analysis of cardiac rehabilitation after conventional heart valve surgery versus usual care

European Journal of Preventive Cardiology

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Abstract

Background: While cardiac rehabilitation in patients with ischaemic heart disease and heart failure is considered cost-effective, this evidence may not be transferable to heart valve surgery patients. The aim of this study was to investigate the cost-effectiveness of cardiac rehabilitation following heart valve surgery.

Design: We conducted a cost–utility analysis based on a randomised controlled trial of 147 patients who had undergone heart valve surgery and were followed for 6 months.

Methods: Patients were randomised to cardiac rehabilitation consisting of 12 weeks of physical exercise training and monthly psycho-educational consultations or to usual care. Costs were measured from a societal perspective and quality-adjusted life years were based on the EQ-5D. [AQ2] Estimates were presented as means and 95% confidence intervals (CIs) based on bootstrapping. Costs and effect differences were presented in a cost-effectiveness plane and were transformed into net benefit and presented in cost-effectiveness acceptability curves.

Results: No statistically significant differences were found in total societal costs (–1609 Euros; 95% CI: –6162 to 2942 Euros) or in quality-adjusted life years (–0.000; 95% CI –0.021 to 0.020) between groups. However, approximately 70% of the cost and effect differences were located below the x-axis in the cost-effectiveness plane, and the cost-effectiveness acceptability curves showed that the probability for cost- effectiveness of cardiac rehabilitation compared to usual care is at minimum 75%, driven by a tendency towards costs savings.

Conclusions: Cardiac rehabilitation after heart valve surgery may not have improved health-related quality of life in this study, but is likely to be cost-effective for society, outweighing the extra costs of cardiac rehabilitation.

Keywords

Cardiac rehabilitation, economic evaluation, cost–utility, heart valve surgery

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Introduction

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Exercise-based cardiac rehabilitation (CR) for patients with ischaemic heart disease (IHD) and heart failure has been investigated, and is considered cost-effec­tive.1,2 These findings may not be transferable to other cardiac populations, including patients undergo­ing heart valve surgery, particularly those without con­comitant IHD. There is limited knowledge on the health care needs following heart valve surgery3 and no studies have investigated the cost-effectiveness of CR for these patients.

Investigating the cost-effectiveness of CR for patients following heart valve surgery is important for several reasons. First, the incidence rates of heart valve diseases and the numbers of heart valve procedures are increasing. Secondly, even though the prevalence of heart valve diseases is low compared to, for example, patients with IHD, their investigation and treatment costs to the health care system are significant.4 Thirdly, health care use and therefore costs are substan­tial following heart valve surgery, with high readmis­sion rates of up to 56% described within the first year post-surgery.5,6 Finally, while health-related quality of life (HRQL) typically improves overall after heart valve surgery,7 HRQL is lower compared to matched general populations at up to 12 months after surgery,5 indicat­ing the potential of CR for these patients.

A recent Danish nationwide survey of patients undergoing heart valve surgery demonstrated no signifi­cant differences in total costs or other categories of pri­mary care visits, inpatient hospital admissions, prescription medication or sick leave costs, and con­cluded that CR, when compared to non-participation, can be considered cost-neutral and may even offset more expensive outpatient visits.8 However, the study contained no information on HRQL or other patient-reported outcomes, which are crucial to informing health policy planning regarding the attractiveness of CR as a routine practice. Within the field of CR, cost–utility ana­lyses are particularly warranted. These are similar to cost-effectiveness analyses, but with quality-adjusted life years (QALYs) as the outcome, simultaneously cap­turing changes in both mortality and HRQL.2

The aim of the current study was to investigate the cost–utility of CR in patients following heart valve sur­gery who were randomised to CR versus usual care.

Methods Study design

We conducted a cost–utility analysis carried out along­side a randomised controlled trial, CopenHeartVR,9 of 147 patients undergoing heart valve surgery who were

randomised to CR (n 1/4 72) or usual care (n 1/4 75). The power calculation was based on the primary outcome of the trial: physical capacity measured by VO2 peak. The original recruitment target was 210. However, due to difficulties in recruitment, a time point for terminat­ing inclusion was established, and a sample size of 147 patients was reached. The power was recalculated before the data analysis of the accrued sample.10 Full details of the trial protocol and ethical approvals,9 as well as the clinical outcomes of the CopenHeartVR trial,10 are available. Briefly, the main finding of the clinical trial was that CR significantly improves VO2peak at 4 months.10 According to current guide­lines, all patients received a physical examination and biochemical and echocardiographic assessment from the referral hospital following surgery.11 Costs and out­comes were evaluated from the date of discharge and until 6 months post-surgery, which was considered an adequate length of follow-up, since costs are mainly incurred within the first months post-surgery,8 and mortality rates are considered low following surgery.4,5

Population, setting and location

Trial participants were recruited at a large Danish University Hospital between February 2012 and May 2014. Inclusion criteria were undergoing elective right-or left-sided conventional heart valve surgery, age 18 years or older and able to speak and understand Danish. Exclusion criteria were IHD, participation in other CR programmes by the time of recruitment, dis­eases complicated by physical activity, participation in competitive sports and pregnancy and/or breastfeeding.9

Study perspective

The study adopted a societal perspective with total soci­etal costs that included intervention costs, follow-up costs in the health care sector (primary and secondary care and prescription medication) and broader costs to society (productivity loss due to long-term sick leave and patient-borne costs associated with CR participation).

Cardiac rehabilitation

Trial participants randomised to CR participated in a 12-week physical exercise training programme with three weekly sessions consisting of graduated cardio­vascular training and strength exercises. One exercise protocol was applied to all participants, but individua­lised where necessary. The programme was initiated at hospital and continued either at a hospital or munici­pality-certified locations (69%) or as home-based train­ing with an exercise cycle ergometer or as self-training in a fitness centre (31%), and some participants chose

to combine the modes of delivery. Alternatively, trial participants randomised to CR instead participated in a psycho-educational intervention consisting of five monthly nurse consultations aimed at improving dis­ease coping by applying a patient-centred approach, which was initiated within the first month after surgery.10

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Usual care

Participants randomised to usual care gave written con­sent agreeing not to participate in structured hospital or municipality service CR. All CR participation outside of the trial protocol was monitored using a 6-month follow-up self-reported questionnaire and subsequent telephone-based contacts.9

Costing

The costs of CR and patient-borne costs were estimated from micro-costing,12 and all other costs were esti­mated from administrative nationwide health care ser­vice registers. All costs were inflated to 2014 Euros using the general consumer price index and a currency conversion rate of 745 DKK 1/4 100 Euros. No discount­ing was undertaken due to the time horizon.

Cardiac rehabilitation costs. The costs of CR included costs associated with physical exercise training, nurse consultations and equipment used for physical exercise training. Equipment included pulse watches provided to participants in the CR group. CR participants elect­ing either a fitness centre or a cycle ergometer for home-based training were required to incur those costs.

Resource use associated with physiotherapist and nurse consultations was estimated based on health care professionals’ time registrations and valued using average wage tariffs, which were loaded with a factor of 1.6 to account for non-productive time. Some partici­pants in the CR group received only physical exercise training or nurse consultations, in which case costs associated with non-participation for either of the elem­ents were valued at 0 Euros. Equipment costs for phys­ical exercise training were estimated using market prices. Overhead costs of 3.1% were allocated.

For participants in the usual care group who, despite written consent, participated in CR outside of the trial protocol, costs were estimated using national tariffs. Based on observations of a national cohort of similar patients undergoing heart valve surgery, it was assumed that those trial participants completed 8.6 physical training sessions.8

Primary health care costs. Resource use in primary health care was obtained from the Danish National Health

Service Register13 and valued using tariffs of the national agreements between the Danish National Health Service and professional associations of medical specialists. We categorised service providers into gen­eral practitioners (codes 80–84, 89), medical specialists (codes 1–21, 23, 24), physiotherapists (codes 51, 62) and psychologists (code 63).

Secondary health care costs. Resource use of secondary health care (in- and out-patient hospital-based services) was derived from the Danish National Patient Registry14 and valued using tariffs of the case-mix system of Diagnosis-Related Grouping (DRG) for inpa­tient admissions and the Danish Ambulatory Grouping System (DAGS) for outpatient contacts. Inpatient admis­sions were categorised as acute or non-acute cardiovascu­lar versus other admissions, and outpatient contacts were categorised as cardiovascular versus other contacts.

Prescription medication costs. Use of prescription medica­tion outside hospitals was extracted from the Danish National Prescription Register.15 Medication was cate­gorised based on Anatomical Therapeutic Chemical classification codes into: antithrombotic agents includ­ing anti-coagulant treatment (B01A); anti-arrhythmic medication (C01BD01, C01BD07); analgesics (M02, N02); psycholeptics (N05A); other cardiovascular medication; and other medication. Medication use was quantified using the defined daily dose16 and valued by the retail price.

Sick leave costs. Sick leave weeks among trial partici­pants who were part of the labour force at baseline were acquired from the national DREAM database and valued using national age- and gender-matched gross wages. [AQ3] Only sick leave lasting for more than 2weeks is registered in the DREAM database.17

Patient-borne costs. Time and costs spent on CR participa­tion were obtained from patient diaries and self-reported questionnaires. In case of missing data, estimates for these sessions were based on average figures from other sessions within the same participants. The duration of sessions typically ranged from 45 to 60 minutes.

Time spent on CR and transportation was valued using the opportunity cost method and based on national average gender- and age-matched net salaries for those who were part of the labour force at baseline. The value of time for those outside the labour force was set to zero in the base case. Costs associated with vehicular transportation to and from CR facilities were estimated by assuming that 1 km of transportation took 1 minute and was valued by the official Danish mileage tariff of 0.28 Euros per kilometre: foot or bicycle transportation costs were valued at 0 Euros.

Quality-adjusted life years

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The EuroQoL EQ-5D-5L instrument18 was used to measure HRQL at baseline and after 6 months of follow-up. [AQ4] Aggregation from the five-level to three-level item responses was conducted based on an established methodology because Danish preference weights are not yet available for the five-level version.19 Danish preference weights were used to calculate utility scores and QALYs.20

Handling of missing data

The EQ-5D-5L instrument responses contained missing data at baseline and 6 months of follow-up distributed unequally between the groups (participants in the CR group: n = 1 at baseline and n =7 at 6 months of follow-up; in the usual care group, the corresponding figures were 11 and 17).

Full QALY calculation was performed for a total of 119 participants (81%), with 118 participants having no missing data at either point in time and one participant in the usual care group dying 3 days after randomisa­tion. Missing data were assumed to be missing at random and handled by inverse probability weighting (IPW) of complete response cases.21 Logistic regression was used to calculate the probability weights and included variables of the randomisation group and hos­pital admissions in the base case, as these variables sig­nificantly explained non-response.

Cost–utility analysis

Resource use, costs and outcomes were presented as means and between-group differences with 95% confi­dence intervals (CIs) based on non-parametric boot­strapping with 5000 replicates.22 For differences in resource use and costs, adjustment was made for sick leave before randomisation because the randomisation procedure was not successful in allocating individuals randomly with respect to this particular characteristic.23

The uncertainties in the cost and QALY estimates were presented in a scatter plot of bootstrapped cost and effect differences. These were transformed into net benefit to generate the cost-effectiveness acceptability curve, which illustrates the probability of CR being cost-effective over usual care for a range of hypothetical threshold values of willingness to pay for a QALY.24 The cost-effectiveness acceptability curve approach was also used for illustrating the results of sensitivity ana­lysis, including alternative scenarios of the valuation of patient time, an alternative IPW model specification including variables considered likely to predict non-response, restriction of the analysis to complete cases alive at 6 months of follow-up and per-protocol analysis.

Results

Baseline characteristics

Baseline characteristics in the 147 randomised trial par­ticipants showed a minor gender imbalance that was considered to occur by chance. However, there was a pre-randomisation difference between groups with regards to sick leave (Table 1), for which the analyses were adjusted. A total of 61/72 (85%) in the CR group

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Table 1. Baseline characteristics. |  |  |  |  |
|  | CR(n = 72) | Usual care (n = 75) |
| Gender |  |  |  |  |
| Male sex (%) | 59 | (82) | 53 | (71) |
| Age (years), (± SD) | 62.0 | (11.5) | 61.0 | (9.9) |
| Marital status |  |  |  |  |
| Married (%) | 52 | (72) | 51 | (68) |
| Employment status |  |  |  |  |
| Employed (%) | 42 | (58) | 45 | (60) |
| Retired (%) | 27 | (38) | 30 | (40) |
| Educational level |  |  |  |  |
| Maximum of 9 school years (%) | 9 | (13) | 7 | (10) |
| High school, vocational training (%) | 47 | (65) | 55 | (73) |
| University degree (%) | 13 | (18) | 13 | (17) |
| Missing (%) | 3 | (4) | 0 |  |
| Annual income (Euros)0–20,000 (%) | 12 | (17) | 10 | (13) |
| 20,000–30,000, (%) | 16 | (22) | 14 | (19) |
| >30,000 (%) | 44 | (61) | 51 | (68) |
| Type of surgery |  |  |  |  |
| Aortic valve surgery (%) | 46 | (64) | 47 | (63) |
| Mitral valve surgery (%) | 27 | (38) | 26 | (35) |
| Pulmonal and tricuspid valve surgery (%) | 1 | (1) | 2 | (3) |
| Cardiac status |  |  |  |  |
| Euroscore II (± SD) | 1.1 | (0.8) | 1.0 | (0.6) |
| LVEF (± SD) | 55.0 | (9.6) | 54.0 | (10.2) |
| NYHA class I–II (%) | 53 | (74) | 52 | (69) |
| NYHA class III–IV (%) | 19 | (26) | 23 | (31) |
| Atrial fibrillation (%) | 15 | (21) | 12 | (16) |
| Hypertension (%) | 28 | (39) | 34 | (45) |
| Diabetes mellitus (%) | 2 | (3) | 7 | (9) |
| Dyslipidaemia (%) | 1 | (1) | 1 | (1) |
| Body mass index (± SD) | 26.2 | (4.2) | 26.1 | (3.9) |
| Pre-surgery sick leave weeks (±SD)a | 1.3 | (8.1) | 2.7 | (5.2) |

Categorical variables are presented as numbers (%) and numerical vari­ables as means (± SD).

aSick leave weeks during 6 months before surgery.

CR: cardiac rehabilitation; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association.

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participated in the exercise training programme with an average number of 28 sessions, and 66/72 (92%) attended the nurse consultations in the CR group with 95% attending at least four consultations (data not shown).

Costs

Resource use and costs of care are presented in Tables 2 and 3, respectively. The total costs in the CR group

were estimated to be 882 Euros per patient. In the usual care group, 13/75 participants received CR out­side of the trial protocol and the costs for these partici­pants were estimated at 132 Euros per patient. Statistically significantly higher CR costs and patient-borne costs were observed in the CR group compared to the usual care group. No statistically significant dif­ferences were observed for health care use, sick leave or associated costs, except for a statistically significant dif­ference in other acute hospital admission costs, which

Table 2. Resource use from heart valve surgery through 6 months of follow-up.

|  |  |  |  |
| --- | --- | --- | --- |
| Resource categories | CR (n 1/4 72) | Usual care (n 1/4 75) | Difference (95% CI)a |
| CR intervention |  |  |  |
| Physiotherapist instruction/training (hours) | 13.00 | 1.24 | 11.99 (9.07; 14.90) |
| Nurse consultations (hours) | 2.76 | 0 | 2.77 (2.49; 3.05) |
| Equipment (n) |  |  |  |
| Pulse watch | 0.83 | 0 | 0.84 (0.76; 0.92) |
| Cycle ergometer (home training) | 0.15 | 0 | 0.15 (0.07; 0.24) |
| Fitness centre fee (home training) | 0.42 | 0 | 0.41 (0.17; 0.65) |
| Primary care (contacts) |  |  |  |
| General practitioners | 14.25 | 16.96 | –2.74 (–7.21; 1.73) |
| Medical specialists | 0.36 | 0.36 | 0.00 (–1.16; 0.16) |
| Physiotherapists | 0.14 | 0.12 | 0.03 (–0.08; 0.14) |
| Psychologists | 0.01 | 0.03 | –0.00 (–0.04; 0.04) |
| Other | 0.74 | 0.88 | –0.16 (–0.48; 0.16) |
| Secondary care |  |  |  |
| Hospital inpatient (admissions) |  |  |  |
| Cardiovascular, acute | 0.67 | 0.84 | –0.17 (–0.63; 0.28) |
| Cardiovascular, not acute | 0.16 | 0.16 | 0.00 (–0.15; 0.17) |
| Other, acute | 0.58 | 0.88 | –0.30 (–0.66; 0.07) |
| Other, not acute | 0.06 | 0.09 | –0.04 (–0.14; 0.06) |
| Bed days | 4.53 | 7.40 | –2.87 (–6.59; 0.84) |
| Hospital outpatient (contacts) |  |  |  |
| Cardiology | 8.13 | 7.80 | 0.53 (–2.11; 3.17) |
| Other | 2.97 | 3.69 | –0.86 (–2.59; 0.88) |
| Pharmaceuticals (DDD) |  |  |  |
| Antithrombotic/anticoagulant | 162.40 | 163.72 | –1.49 (–34.60; 31.61) |
| Anti-arrhythmics | 16.81 | 26.27 | –8.23 (–25.71; 9.23) |
| Analgesics | 12.84 | 27.37 | –13.14 (–28.44; 1.73) |
| Psycholeptics | 13.30 | 10.56 | 2.18 (–11.93; 16.28) |
| Other cardiovascular medication | 447.89 | 476.95 | –47.83 (–193.40; 97.73) |
| Other medication | 149.06 | 168.05 | –18.48 (–81.34; 44.38) |
| Production lossSick leave (weeks) | 4.22 | 7.40 | –1.35 (–3.47; 0.77) |
| Patients’ resource use |  |  |  |
| Transportation (km) | 435.68 | 30.69 | 412 (290.57; 535.19) |
| Hours (CR participation and transportation) | 30.04 | 2.00 | 28.35 (24.21; 32.50) |

Values are mean numbers of resource units and mean differences (95% CI). aAdjustments made for pre-sick leave weeks before randomisation.

CI: confidence interval; CR: cardiac rehabilitation; DDD: defined daily dose.

|  |  |  |  |
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| Table 3. Costs from heart valve surgery through 6 months of follow-up (Euros). |
| Resource categories | CR (n 1/4 72) | Usual care (n 1/4 75) Difference (95% CI)a |
| CR intervention |  |  |  |
| Physiotherapist instruction/training | 634 | 128 | 515 (361; 669) |
| Nurse consultations | 146 | 0 | 147 (132; 161) |
| Equipment |  |  |  |
| Pulse watch | 21 | 0 | 21 (19; 23) |
| Cycle ergometer (home training) | 41 | 0 | 41 (18; 63) |
| Fitness centre fee (home training) | 14 | 0 | 14 (6; 22) |
| Overheads | 26 | 4 | 23 (18; 27) |
| Total CR costs | 882 | 132 | 758 (602; 914) |
| Primary care |  |  |  |
| General practitioners | 321 | 327 | –2 (–82; 77) |
| Medical specialists | 51 | 52 | –3 (–35; 29) |
| Physiotherapists | 28 | 15 | 15 (–16; 46) |
| Psychologists | 9 | 6 | 7 (–15; 29) |
| Other | 51 | 56 | –5 (–26; 17) |
| Total primary care costs | 460 | 456 | 12 (–85; 108) |
| Secondary care |  |  |  |
| Hospital inpatient |  |  |  |
| Cardiovascular, acute | 3794 | 3551 | 221 (–2640; 3082) |
| Cardiovascular, not acute | 784 | 785 | 9 (–886; 904) |
| Other, acute | 1751 | 3316 | –1447 (–2803; –90) |
| Other, not acute | 134 | 570 | –418 (–1154; 317) |
| Total inpatient costs | 6463 | 8223 | –1634 (–5798; 2528) |
| Hospital outpatient |  |  |  |
| Cardiology | 1389 | 1186 | 212 (–186; 610) |
| Other | 669 | 742 | –107 (451; 237) |
| Total outpatient costs | 2059 | 1929 | 105 (–409; 619) |
| Pharmaceuticals |  |  |  |
| Antithrombotic/anticoagulant | 67 | 72 | 1 (–28; 30) |
| Anti-arrhythmics | 3 | 5 | –2 (–5; 1) |
| Analgesics | 7 | 8 | –1 (–8; 6) |
| Psycholeptics | 5 | 14 | –10 (–36; 15) |
| Other cardiovascular medication | 52 | 72 | –25 (–55; 5) |
| Other medication | 79 | 95 | –21 (–70; 29) |
| Total pharmaceutical costs | 213 | 266 | –58 (–138; 21) |
| Total health care costs Production loss | 9360 | 12036 | –2593 (–7144; 1958) |
| Sick leave | 3799 | 6432 | –1110 (–2999; 781) |
| Patient-borne costs |  |  |  |
| Transportation expenses | 109 | 9 | 104 (69; 138) |
| Time (CR participation and transportation) | 199 | 2 | 212 (142; 282) |
| Total patent borne costs | 309 | 10 | 316 (228; 403) |
| Total societal costs | 14185 | 17448 | –1609 (–6162; 2942) |

Values are mean costs and mean differences (95% CI). aAdjustments made for pre-sick leave costs before randomisation. CI: confidence interval; CR: cardiac rehabilitation,

was due to a higher number of hospital admissions in the usual care group and to extreme cost observations. The overall societal costs per patient were estimated at 14,185 Euros in the CR group and at 17,448 Euros in

the usual care group, leading to a non-significant dif­ference of –1609 Euros (95% CI: –6162 to 2942) in favour of the CR group, which was driven by lower hospital admission and sick leave costs. [AQ5]

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Outcomes

No statistically significant differences in EQ-5D HRQL scores or QALYs were found between the groups based on either complete response analysis or on the weighted complete response analysis (Table 4).

Cost–utility

The cost and QALY differences were located in all four quadrants of the scatter plot, which indicates substan­tial uncertainty about the cost-effectiveness of CR (Figure 1a). As approximately 70% of the cost and

QALY differences were located below the x-axis, CR has a high probability of being cost-saving. However, cost and QALY differences were also spread almost equally to the left and right of the y-axis, suggesting that CR holds only a 50% probability of providing a better outcome.

The cost-effectiveness acceptability curves for the base case analysis and for the sensitivity analysis including alternative scenarios showed a similar trend, namely that the probability for cost-effectiveness is at minimum 75% and does not increase for increasing values of willingness to pay due to the lack of a QALY benefit of CR (Figure 1b). The probability for

Table 4. Outcomes at 6 months of follow-up.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | CR (n 1/4 72) |  | Usual care (n 1/4 75) | Difference (95% CI) |
| n | Mean | n | Mean |
| EQ-5D |  |  |  |  |  |
| Baseline | 71 | 0.714 | 64 | 0.696 | 0.017 (–0.023; 0.058) |
| 6 months | 65 | 0.889 | 58 | 0.919 | –0.029 (–0.071; 0.012) |
| Differencea | 65 | 0.175 | 53 | 0.226 | –0.051 (–0.098; –0.003) |
| Died | 72 | 0 | 75 | 0.013 | –0.013 (–0.033; 0.006) |
| QALYs |  |  |  |  |  |
| Complete response | 65 | 0.401 | 54 | 0.399 | 0.002 (–0.021; 0.025) |
| Weighted complete responseb | 65 | 0.400 | 54 | 0.401 | –0.000 (–0.021; 0.020) |

Values are mean scores and mean differences (95% CI).

aBased on responses at both baseline and at 6 months.

bBased on inverse probability weights accounting for variables significantly explaining non-response (randomisation group and number of hospital

admissions during follow-up).

CI: confidence interval; CR: cardiac rehabilitation; EQ-5D: EuroQoL 5 Dimensions; QALY: quality-adjusted life year.

Figure 1. (a) Bootstrapped replicates of differences in costs and quality-adjusted life years (QALYs) between cardiac rehabilitation and usual care. (b) Cost-effectiveness acceptability curves for alternative scenarios. IPW: inverse probability weighting.



(a)

Cost difference (Euros)

-10000 -5000 0 5000 10000

–.04 –.02

QALY difference

.02 .04

(b)

Probabilty

0 .5 1

0 50000 100000

Base case Alternative IPW model

Dead person excluded Value of time for all set to net salary Per protocol analysis

Threshold for willingness-to-pay (Euros)

cost-effectiveness is thus driven largely by the observed tendency for societal cost savings. The most significant impact of the sensitivity analysis was demonstrated by the per-protocol analysis, in which the maximum prob­ability for cost-effectiveness reached 90%.

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Discussion Study findings

We investigated the cost–utility of a CR programme for patients following heart valve surgery using data from a randomised trial, CopenHeartVR,10 which is the largest such trial to date, with CR programme costs estimated at 882 Euros and patient-borne CR costs estimated at 309 Euros. No statistically significant differences were found between the groups for costs or QALYs, but due to a tendency for societal cost savings when CR is pro­vided, the probability for cost-effectiveness is in favour of CR.

Comparison with other studies

This study is the first investigation of the cost–utility of CR among patients undergoing heart valve surgery. Previous CR studies suggest that the cost–utility of hospital-based CR versus usual care among patients with myocardial infarction is between $650/QALY25 and $9200/QALY.26 In addition, the mode of delivery has been examined for patients with IHD. Costs per QALY of between $0 and $11,400 have been reported for hospital-based versus home-based CR.2 Cost– consequence analyses support both hospital and home-based CR as equally cost-effective or cost-saving interventions compared to usual care in coron­ary and heart failure patients.2 In this study, we cannot discern whether the modalities involved may have influ­enced the results of the analysis.

A systematic review of the cost-effectiveness studies of CR demonstrates a variety of study perspectives, CR interventions, comparators and lengths of follow-up, making comparison across studies difficult,2 but importantly, unlike these studies, we did not find an effect of CR on HRQL. This could have several explan­ations. The timing and the intensity of CR and, in par­ticular, the psycho-educational intervention may not be adequate for patients following heart valve surgery. Overall, CR was initiated 4 weeks after surgery, which we believe may have been too late for this population in which high levels of complications and readmissions frequently occur within the first months following sur­gery.5 Future studies should evaluate CR interventions with some components having already been initiated post-discharge. The level of adherence to CR was rela­tively high in our study compared to previously

reported levels in a real-life setting.27 The length of follow-up in our study was shorter than some of the studies conducted among patients with IHD.2 In regard to costs, a time horizon of 6 months from surgery was considered adequate since costs were mainly incurred within the first months after discharge in our popula­tion, as was demonstrated in a non-randomised but nationwide cost analysis of consecutive patients undergoing heart valve surgery.8

Strengths, limitations and external validity of the study

The strengths of this study include randomisation to the CR intervention and complete information on costs with no losses to follow-up based on multiple registers. Further, none of the alternative scenarios included in the sensitivity analysis altered the overall findings.

There are several limitations to the study. Sample size calculations for the clinical trial were based on the primary outcome (improvement in VO2 peak),10 the economic evaluation was conducted alongside the clinical trial and a large proportion of patients declined to participate in the trial. The numbers of patients were unequal in the groups due to the early termination of the trial.10 However, the drop-out rates in the two groups were also uneven, and therefore we do not believe that the difference in the number of patients in the groups at baseline significantly impacted the results.

In both groups, baseline EQ-5D scores were high, indicating that this population may not be representa­tive of heart valve surgery patients broadly. Future studies should investigate the cost and effects of CR in specific groups of patients undergoing heart valve surgery that may benefit from CR differently, such as elderly patients with aortic stenosis or patients with different levels of functional capacity, or such studies should include a larger sample of patients in order to allow for subgroup analyses. In addition, studies with longer follow-up periods are recommended.

The EQ-5D instrument may not be suitable for out­come assessment in this population, which, to some extent, experiences spontaneous recovery, but may also experience problems at 6 months that are not cap­tured by generic HRQL instruments. Further, a consid­erable minority of the usual care group (17.3%) participated in CR. However, the per-protocol analysis did not alter the overall finding of the study. Missing outcome data were handled through analyses of com­plete cases and by IPW of these and were tested in alternative scenario models. Finally, the study was con­ducted in a Danish context, which limits generalisation to other countries.

Conclusion

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Even though CR following heart valve surgery in these Danish patients did not improve short-term HRQL for the patients, it does hold a high probability of being cost-effective for society due to fewer hospital inpatient admissions and less sick leave, which outweigh the extra costs of CR.

Author contribution

TBH, ADZ, SKB, NO and RS contributed to the design of the work. TBH, ADZ, SKB, KLS, LCT, NO and RS con­tributed to the acquisition, analysis or interpretation of data. TBH and RS drafted the manuscript. All authors critically revised the manuscript and gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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References

1. Papadakis S, Oldridge NB, Coyle D, et al. Economic evaluation of cardiac rehabilitation: A systematic review. Eur J Cardiovasc Prev Rehabil 2005; 12: 513–520.
2. Wong WP, Feng J, Pwee KH, et al. A systematic review of economic evaluations of cardiac rehabilitation. BMC Health Serv Res 2012; 12: 243.
3. Chambers JB, Shah BN, Prendergast B, et al. Valvular heart disease: A call for global collaborative research ini­tiatives. Heart 2013; 99: 1797–1799.
4. Coffey S, Cairns BJ and Iung B. The modern epidemiology of heart valve disease. Heart 2016; 102: 75–85.
5. Sibilitz KL, Berg SK, Thygesen LC, et al. High readmis­sion rate after heart valve surgery: A nationwide cohort study. Int J Cardiol 2015; 189: 96–104.
6. Trochu JN, Le Tourneau T, Obadia JF, et al. Economic burden of functional and organic mitral valve regurgita­tion. Arch Cardiovasc Dis 2015; 108: 88–96.
7. Goldsmith IR, Lip GY and Patel RL. A prospective study of changes in the quality of life of patients following mitral valve repair and replacement. Eur J Cardiothorac Surg 2001; 20: 949–955.
8. Hansen TB, Zwisler AD, Berg SK, et al. Exercise-based cardiac rehabilitation after heart valve surgery: Cost analysis of health care use and sick leave. Open Heart 2015; 2: 1.
9. Sibilitz KL, Berg SK, Hansen TB, et al. Effect of com­prehensive cardiac rehabilitation after heart valve surgery (CopenHeartVR): Study protocol for a randomised clin­ical trial. Trials 2013; 14: 104.
10. Sibilitz KL, Berg SK, Rasmussen TB, et al. Cardiac rehabilitation increases physical capacity but not mental health after heart valve surgery: Results of the rando­mised CopenHeartVR trial. Heart 2016; 102: 1995–2003.
11. Butchart EG, Gohlke-Bãrwolf C, Antunes MJ, et al. Recommendations for the management of patients after heart valve surgery. Eur Heart J 2005; 26: 2463–2471.
12. Frick KD. Microcosting quantity data collection meth­ods. Med Care 2009; 47(Suppl.): S76–S81.
13. Andersen JS, Olivarius NF and Krasnik A. The Danish National Health Service Register. Scand J Public Health 2011; 39(Suppl.): 34–37.
14. Lynge E, Sandegaard JL and Rebolj M. The Danish National Patient Register. Scand J Public Health 2011; 39(Suppl.): 30–33.
15. Wallach Kildemoes H, Toft Sørensen H and Hallas J. The Danish National Prescription Registry. Scand J Public Health 2011; 39(Suppl.): 38–41.
16. WHO Collaborating Centre for Drug Statistics Methodology. Defined daily dose (DDD): Definition and general considerations. <http://www.whocc.no/ddd/> definition\_and\_general\_considera/ (Accessed September 2015).
17. Stapelfeldt C, Jensen C, Andersen N, et al. Validation of sick leave measures: Self-reported sick leave and sickness benefit data from a Danish national register compared to multiple workplace-registered sick leave spells in a Danish municipality. BMC Public Health 2012; 12: 661.
18. Devlin NJ and Krabbe PFM. The development of new research methods for the valuation of EQ-5D-5L. Eur J Health Econ 2013; 14(Suppl.): S1–S3.
19. EuroQoL. EQ-5D-5L value sets. <http://www.euroqol>. org/about-eq-5d/valuation-of-eq-5d/eq-5d-5l-value-sets. html (Accessed September 2015).
20. Wittrup-Jensen KU, Lauridsen JT, Gudex C, et al. Estimating Danish EQ-5D tariffs using TTO and VAS. In: Norinder A, Pedersen K and Roos P (eds) Proceedings of the 18th Plenary Meeting of the Euro-Qol Group, 1st ed. Copenhagen: IHE, The Swedish Institute for Health Economics, 2002, pp.257–295.
21. Seaman SR and White IR. Review of inverse probability weighting for dealing with missing data. Stat Methods Med Res 2013; 3: 278–295.
22. Carpenter J and Bithell J. Bootstrap confidence intervals: When, which, what? A practical guide for medical statis­tics. Stat Med 2000; 19: 1141–1165.
23. Manca A, Hawkins N and Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. Health Econ 2005; 14: 487–496.
24. Fenwick E, O’Brien BJ and Briggs A. Cost-effectiveness acceptability curves – Facts, fallacies and frequently asked questions. Health Econ 2004; 13: 405–415.
25. Yu CM, Lau CP, Chau J, et al. A short course of cardiac rehabilitation programme is highly cost effective in improving long-term quality of life in patients with

recent myocardial infarction or percutaneous coronary intervention. Arch Phys Med Rehabil 2004; 85: 1915–1922.

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26. Oldridge N, Furlong W, Feeny D, et al. Economic evalu­ation of cardiac rehabilitation soon after acute myocar­dial infarction. Am J Cardiol 1993; 72: 154–161.

27. Hansen TB, Berg SK, Sibilitz LK, et al. Availability of, referral to and participation in exercise-based cardiac rehabilitation after heart valve surgery: Results from the national CopenHeart survey. Eur J Prev Cardiol 2015; 22: 6170–6718.