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ORIGINAL REPORT

IMPLANTABLE CARDIOVERTER DEFIBRILLATOR SPECIFIC REHABILITATION IMPROVES HEALTH COST OUTCOMES: FINDINGS FROM THE COPE-ICD RANDOMIZED CONTROLLED TRIAL

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Objective: The Copenhagen Outpatient Programme – implantable cardioverter defibrillator (COPE-ICD) trial included patients with implantable cardioverter defibrillators in a randomized controlled trial of rehabilitation. After 6–12 months significant differences were found in favour of the rehabilitation group for exercise capacity, general and mental health. The aim of this paper is to explore the long-term health effects and cost implications associated with the rehabilitation programme; more specifically, (i) to compare implantable cardioverter defibrillator therapy history and mortality between rehabilitation and usual care groups; (ii) to examine the difference between rehabilitation and usual care groups in terms of time to first admission; and (iii) to determine attributable direct costs.

Methods: Patients with first-time implantable cardioverter defibrillator implantation ($n=196$) were randomized (1:1) to comprehensive cardiac rehabilitation or usual care. Outcomes were measured by implantable cardioverter defibrillator therapy history from patient records and national register follow-up on mortality, hospital admissions and costs.

Results: No significant differences were found after 3 years for implantable cardioverter defibrillator therapy or mortality between rehabilitation and usual care. Time to first admission did not differ. The cost of rehabilitation was 335 USD/276 Euro per patient enrolled in rehabilitation. The total attributable cost of rehabilitation after 3 years was –6,789 USD/–5,593 Euro in favour of rehabilitation.

Conclusion: No long-term health outcome benefits were found for the rehabilitation programme. However, the rehabilitation programme resulted in a reduction in total attributable direct costs.

Key words: implantable cardioverter defibrillator; rehabilitation; economics.

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INTRODUCTION

Comprehensive cardiac rehabilitation that includes both exercise training and psycho-educational components is recommended for patients with various heart conditions (1). However, evidence from studies of patients with complex conditions, such as those with an implantable cardioverter defibrillator (ICD), is sparse (2).

The Copenhagen Outpatient Programme – implantable cardioverter defibrillator (COPE-ICD) trial, initiated in 2007, included 196 ICD patients in a randomized controlled trial (RCT) on rehabilitation. The comprehensive cardiac rehabilitation intervention consisted of an exercise training component and a psycho-educational component. Primary and secondary outcome analyses after 6–12 months showed significantly increased VO_2 after exercise training compared with usual care (mean 23.0 (95% confidence interval (95% CI) 20.9–22.7) vs 20.8 ml/min/kg (95% CI 18.9–22.7) in the control group ($p=0.004$)). Furthermore, comprehensive cardiac rehabilitation significantly increased general health and mental health compared with usual care (3).

Rehabilitation trials often evaluate intermediate or surrogate outcomes, such as VO_2 , if they are too short-term to capture all the major health effects and resource implications associated with the treatment (4). In ICD rehabilitation, evidence of reduced risk of ventricular arrhythmia or ICD shock therapy is called for (5). Furthermore, hospitalization and healthcare costs have seldom been measured (2). Such long-term *post-hoc* analyses were pre-planned for the COPE-ICD trial (6).

The objective of this paper is to examine the 3-year long-term effects of a comprehensive cardiac rehabilitation programme for first-time ICD recipients from the COPE-ICD trial (6); more specifically, to: (i) compare ICD therapy history and mortality between rehabilitation and usual care groups; (ii) to examine the difference between rehabilitation and usual care groups in time to first admission; and (iii) to determine attributable direct costs.

METHODS

The design and methods of the COPE-ICD trial have been described in detail elsewhere (6) and are outlined briefly below.

Setting and intervention

The COPE-ICD trial was conducted in a large university hospital with a volume of approximately 300 first-time ICD implantations each year during the trial period. Inclusion criteria were: patients who received a first-time ICD implant and agreed to participate in the entire programme. The intervention included a comprehensive, disease-specific cardiac rehabilitation approach, with exercise-training and psycho-education in addition to usual care. Patients were randomized in a 1:1 ratio to rehabilitation or usual care.

The approach for the psycho-educational part of the intervention was inspired by Parse's human becoming practice methodologies (7). The topics discussed were: events and experiences leading up to the ICD implantation, present thoughts and questions, implications for everyday life, avoidance behaviour, exercise training, impact on family, information (including technical) and recommendations, shock and phantom shock, body image, driving and sexuality. The patients consulted the nurse in person or by phone once a month for 6 months, and every 2 months thereafter for the following 6 months. The psycho-educational part of the intervention was performed by 2 nurses, each with 10 years of clinical experience in the care of patients with ICDs. Three months after the ICD implantation, patients began to participate in training sessions twice a week for a 12-week period. The physical training programme consisted of an individual consultation with a physiotherapist and an individually tailored training programme. Patients in the control group followed a usual care programme, which included medical follow-up and an invitation to participate in a 2-h group session including information about the ICD and exchange of experiences among patients.

All patients in the comprehensive cardiac rehabilitation group participated in the exercise training component of the programme: 46% exercised in hospital, 26% outside the hospital, and 28% did both. A total of 66% of the patients in the usual care group participated in a physical training programme, 17% participated in an exercise programme at a local hospital, 41% participated in exercise training outside the hospital, and 8% did both. Trial discontinuation did not differ significantly between the intervention and usual care group (28.8% vs 30.3% drop-outs; $p=0.64$).

Because of the nature of rehabilitation, the interventions were open-labelled to the staff and the patients. A blinded investigator performed data collection and administration. Blinded outcome analyses were conducted.

Outcomes

Descriptive information on age, sex, marital status and citizenship was available through national registers. Information on comorbidity was obtained from the Danish National Patient Register (NPR) (8), which holds information on all admissions to all Danish hospitals since 1977. We calculated the Tu comorbidity index (9) utilizing information on primary and secondary diagnoses from all in- and out-patient contacts 10 years before the index admission. The following diseases are included in the Tu score: congestive heart failure, cardiogenic shock, arrhythmia, pulmonary oedema, malignancy, diabetes, cerebrovascular disease, acute/chronic renal failure, chronic obstructive pulmonary disease. All diagnoses are weighted equal.

Information on ICD indication and disease demographics for participants was available from patient records.

Implantable cardioverter defibrillator therapy. ICD therapy history was found in patient records up to June 2013. Data registration and analysis was blinded. Programming of ICD therapy was done according to local practice. Ventricular arrhythmias, anti-tachycardia pacing (ATP) and shock therapy were assessed from the time of randomiza-

tion in 2007–2009 until May 2013. ICD therapy during the first 30 days after ICD implantation was not included, since the intervention had not started. All therapies were initially evaluated by a trained technician and, subsequently, by an electro-physiologist with special competences in device therapy. Only appropriate therapy was included. In the assessment of appropriate vs inappropriate therapy, standard clinical criteria were used, including A-V relationship (if available), morphology, regularity of V-signals, and onset of tachycardia.

Mortality and hospital admissions. Information on vital status was available through the Civil Registration System (10) up to June 2013. Admissions after the first 30 days following randomization were available through the NPR. We followed the participants for 3 years and measured and evaluated short-term (1 year) and long-term (3 years) effects on admissions. We obtained information on all admissions, first admission, first acute (non-elective) admission and first acute heart-related admission, including only admissions with an International Classification of Diseases – 10th edition (ICD-10): I00–I99 diagnosis.

Costs. Costs attributable to the intervention were calculated by measuring time spent on an average patient in the intervention group, priced by the salaries of nurses, physicians and physiotherapists (salaries include pension and vacation allowances). A category of other variable costs was included (purchase of pulse watches and T-shirts for use during the training programme). The calculation only considers operational costs and does not include production loss, cost of transportation or the costs of buildings (rent) and equipment.

An estimate of the 3-year cost of hospitalization, outpatient treatment (including emergency ward visits), and care in the primary sector (general practitioner, physiotherapist and psychologist) for both the cardiac rehabilitation group and the usual care group are made. The net costs are given by the difference between average costs in the 2 groups.

The NPR was used to measure the costs of hospital services (hospitalization, outpatient treatment and emergency ward visits). The NPR contains information on a mean price-rate measured by Diagnosis Related Groups (DRG) for each contact with hospitals.

Primary sector costs were measured by use of The Danish National Health Service Register (11), which contains information on services performed in primary care by practitioners, specialists, physiotherapists, chiropractors, etc., which are fully or partially financed by public funding. Data on general practitioners, physiotherapists and psychologists are included in the analysis.

Costs are measured at 2007 prices by use of price indices on health sector costs from Statistics Denmark. Since the study period is 3 years, second and third year costs are discounted to present values by a discount factor of 3%. All costs were measured in 2007 Danish kroner, but were translated into US Dollar Purchasing Power Parities (USD-PPP) and Euro Purchasing Power Parity (EURO-PPP) by use of Organisation for Economic Co-operation and Development (OECD) state extracts. PPP is used in order to take into account the differences in prices between countries.

Statistical methods

Categorical variables are presented as frequencies and percentages. Continuous variables are presented as mean and standard deviation (SD). Baseline data are presented as similarities across groups by number and percentage. As recommended, no significant test for detecting baseline differences was performed (12, 13).

Comparison of mortality and ICD therapy history was performed by χ^2 -test for categorical variables and Mann-Whitney U testing for non-symmetrical variables.

Time to first admission (general, acute or acute heart-related) was analysed by Kaplan–Meier survival analyses and the log-rank test.

Since cost-data are skewed to the right, the 95% confidence interval (95% CI) was computed by use of a non-parametric bootstrap analysis (1,000 replications).

All statistical analyses were conducted using SAS 9.3 software.

Ethics

Patients gave their written informed consent after receiving oral and written information. All data was treated in confidence and patients were assured anonymity. The trial followed the recommendations of the Declaration of Helsinki II. The trial was approved by the regional ethics committee (j.nr. H-B-2007-014), The Danish Data Protection Agency (j.nr. 2007-41-0932) and registered at ClinicalTrials.gov (ID: NCT00569478).

RESULTS

During the inclusion period, October 2007 to November 2009, 589 patients received a first-time ICD implantation at the setting. A total of 196 patients were included, 99 randomized to the comprehensive cardiac rehabilitation and 97 to usual care (Fig. 1).

The baseline demographics and clinical characteristics of the participants (rehabilitation and usual care groups) are presented (Table I).

Rehabilitation vs usual care. The number of ICD shocks delivered did not differ significantly between rehabilitation and usual care groups; a mean of 0.6 vs 0.5 shocks ($p=0.90$). Likewise, no significant difference was found in ventricular tachycardia/ventricular fibrillation or ATP (Table II).

No significant difference was found in mortality, with 19.2% in the rehabilitation group and 12.4% in the control group ($p=0.19$), and no difference in time to death ($p=0.19$). Measuring time to first admission in the total population, 39.8% had a hospitalization within 1 year and 67.9% within 3 years. No difference was found between groups in number of patients with first admission (70 vs 63 patients) ($p=0.35$) (Table III). No significant difference was found in number of admissions: intervention 2.6 vs control 3.2 ($p=0.42$) (not shown). Likewise, no significant difference was found in length of hospital stay between groups: intervention 14.3 vs control 13.2 ($p=0.19$) (not shown).

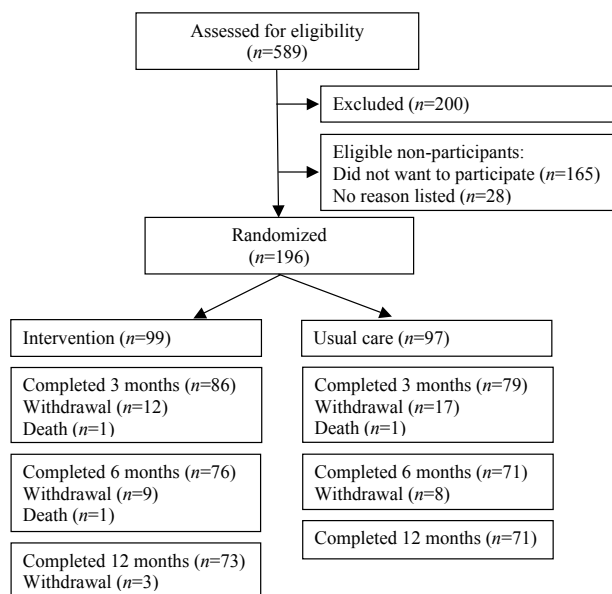


Fig. 1. CONSORT (Consolidated Standards of Reporting Trials) flow-chart.

Table I. Demographic and clinical characteristics

	Intervention (n=99)	Usual care (n=97)
Female, n (%)	20 (20.2)	20 (20.6)
Age, years, mean (SD)	57.6 (12.9)	56.7 (13.5)
14–49 years, n (%)	24 (24.2)	24 (24.7)
50–59 years, n (%)	24 (24.2)	25 (25.8)
60–69 years, n (%)	31 (31.3)	35 (36.1)
70–86 years, n (%)	20 (20.2)	13 (13.4)
Civil status, n (%)		
Married	58 (58.6)	58 (59.8)
Divorce	16 (16.2)	13 (13.4)
Unmarried	16 (16.2)	21 (21.7)
Widowed	9 (9.1)	5 (5.2)
LVEF, mean, (SD) 73% of total population <35	32.2 (17)	32.7 (18)
NYHA class (n %)		
I	30 (30.3)	18 (18.6)
II	42 (42.4)	44 (45.4)
III	24 (24.2)	32 (33.0)
IV	2 (2.0)	1 (1.0)
6-Min Walk Test, mean (SD)	420.2 (112.1)	414.7 (118.0)
VO ₂ (est), mean (SD)	20.98 (7.98)	20.88 (7.8)
Body mass index > 30 (kg/m ²), n (%)	24 (24.2)	19 (19.6)
Diseases, n (%)		
Atrial fibrillation	27 (27.3)	21 (21.7)
CRT device	14 (14.1)	9 (9.3)
History of ischaemic heart disease	45 (45.5)	57 (58.8)
History of heart failure	76 (76.8)	73 (75.3)
Hypertension	18 (18.2)	23 (23.7)
Diabetes mellitus	12 (12.1)	10 (9.7)
TU comorbidity index, n (%)		
Tu 0	1 (1.0)	2 (2.1)
Tu 1	26 (26.3)	27 (27.8)
Tu 2	47 (47.5)	53 (54.6)
Tu 3–6	25 (25.3)	15 (15.5)
Indication, n (%)		
Primary prophylactic	63 (63.6)	67 (69.1)
Secondary prophylactic	36 (36.4)	30 (30.9)
Ventricular fibrillation		
No	75 (75.8)	78 (80.4)
Yes	21 (21.2)	19 (19.6)

Variables used to calculate TU scores are drawn from registers, while all other disease demographics are drawn from patient records. SD: standard deviation; LVEF: Left Ventricular Ejection Fraction; NYHA: New York Heart Association Class; VO₂(est) Estimated Oxygen Consumption; CRT: Cardiac Resynchronization Therapy.

Table II. Comparison of implantable cardioverter defibrillator (ICD) therapy history and deaths between comprehensive cardiac rehabilitation patients and usual care patients from inclusion up to June 2013. Mean follow-up 3.9 years

	Intervention		Usual care		P ^a
	Mean (SD)	Q3, P95	Mean (SD)	Q3, P95	
VT/VF	6.4 (28.7)	2, 13	7.8 (37.3)	1, 28	0.57
ATP	8.4 (37.0)	2, 29	13.8 (92.5)	1, 28	0.29
ICD shocks	0.6 (2.0)	0, 4	0.5 (1.5)	0, 3	0.90
	n (%)		n (%)		P ^b
Deaths	19 (19.2)		12 (12.4)		0.19

^aMann-Whitney U testing whether the 2 distributions differ only with respect to the median. ^bχ² test. VT: ventricular tachycardia; VF: ventricular fibrillation; ATP: anti-tachycardia pacing; SD: standard deviation; Q3: upper quartile; P95: 95% percentile.

Table III. Time to first admission, first acute admission and first acute heart admission

	Intervention n (%)	Usual care n (%)	p-value ^a
Time to first admission, days			
1 year	41 (41.4)	37 (38.1)	0.53
3 year	70 (70.7)	63 (65.0)	0.35
Time to first acute admission, days			
1 year	34 (34.3)	32 (33.0)	0.56
3 year	57 (57.6)	51 (52.6)	0.19
Time to first acute heart admission, days			
1 year	26 (26.3)	24 (24.7)	0.37
3 year	42 (42.4)	42 (43.3)	0.40

^aLog-rank test for intervention group vs usual care group.

The total cost of the intervention was 335 USD-PPP/276 Euro-PPP per patient enrolled in rehabilitation. The total direct cost after 3 years in the rehabilitation groups was 19,664 USD-PPP/16,199 Euro-PPP vs 26,453 USD-PPP/21,792 Euro-PPP in the control group. The total attributable cost of the intervention after 3 years was -6,789 USD-PPP/-5,593 Euro-PPP (Table IV).

DISCUSSION

As previously reported by Berg et al. (3), significant differences were found between groups in physical capacity and mental health after rehabilitation. The aim of this paper was to explore the long-term health effects and cost implications

Table IV. Net costs of rehabilitation 2007 USD-PPP/Euro-PPP

	Costs per person		
	Rehabilitation (n=99)	Usual care (n=97)	Attributable costs (95% CI)
Costs of rehabilitation			
USD-PPP	335		335
Euro-PPP	276		276
Hospitalization			
USD-PPP	12,955	20,061	7,106 (-20,595 to 2,654)
Euro-PPP	10,672	16,526	5,854 (-16,966 to 2,187)
Outpatient treatment (inc. ER visits)			
USD-PPP	5,825	5,668	157 (-1,351 to 1,768)
Euro-PPP	4,799	4,669	129 (-1,113 to 1,456)
General			
Practitioner			
USD-PPP	501	539	-38 (-161 to 83)
Euro-PPP	413	444	-31 (-133 to 69)
Physiotherapist			
USD-PPP	16	157	-141 (-278 to -28)
Euro-PPP	13	129	-116 (-229 to -23)
Psychologist			
USD-PPP	33	28	5 (-44 to 56)
Euro-PPP	27	23	4 (-36 to 46)
Total direct costs			
USD-PPP	19,664	26,453	-6,789
Euro-PPP	16,199	21,792	-5,593

PPP: Purchasing Power Parities; 95% CI: 95% confidence interval; ER: emergency room.

associated with the rehabilitation programme. Looking at the 2 groups, rehabilitation and usual care, the long-term follow-up revealed no difference in ICD shock, mortality or time to first admission between the groups. The total attributable cost of the intervention was -6,789 USD-PPP/-5,593 Euro-PPP in favour of the intervention.

Implantable cardioverter defibrillator therapy shock

No difference was found in ATP or ICD shock, which is in accordance with previous findings in combined programmes (14) and from psycho-educational ICD programmes (15-19). Looking at the exercise-only programmes, the evidence is somewhat conflicting, as the large trial Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) ($n=1,285$ ICD patients) found no difference in ICD shock (20, 21), but a smaller ($n=82$) non-randomized trial found non-participation in outpatient rehabilitation to be a predictor for ICD shock (odds ratio (OR) 4.6, 95% CI 1.5-17.8, $p<0.05$) (22). Davis et al. adjusted for exercise limitation, but not for other co-morbidities that might have confounded the data in the non-randomized design. A randomized trial by Belardinelli ($n=52$) of exercise vs no exercise found that 8 patients in the control group had sustained VT, while no VT events were found in the intervention group (23).

Mortality

Examining mortality, we found no difference between the groups, which matches previous findings (20, 23). However, findings from Ischemic rehabilitation show that a one metabolic equivalent (MET) higher level of maximal aerobic capacity (equivalent to 1 km/h faster running) was associated with a 13% reduction in mortality (24). Several possible explanations exist for not obtaining the same positive effect in ICD patients. In the present trial the difference between the 2 groups after exercise was 0.6 MET, which might not have been enough to have an effect on mortality. Furthermore, the difference between the 2 groups was diluted, since the usual care group exercised on their own, which may explain the limited effect (3). Furthermore, the cardiac disease, which indicated for ICD implantation, may vary and may determine an inhomogeneous response to physical and psycho-educational training.

Admissions

Readmission is considered an indicator of morbidity and quality and efficiency of care and, from the literature on heart failure, we know that patient education and home-based follow-up reduces readmissions (25). We found no difference in time to first admission. None of the previous ICD rehabilitation trials reported time to first admission. However, in the RCT by Dunbar et al. no difference was found in the number of emergency department visits and hospitalizations after 12 months (19), which is in accordance with our findings. In the heart failure literature readmission rates after 6 months are as high as 45%; we found a rate of 39.8% after 1 year and 67.9% after 3 years.

Costs

The total cost of the intervention was 335 USD-PPP/276 Euro-PPP per patient. This cost is relatively low compared with previous findings of the mean cardiac rehabilitation costs of 3,671 in 2003-USD (4,139 in 2007-USD) (26). Oldridge et al. found a cost of 1,365 in 2003-USD (1,539 in 2007-USD) for a combined exercise and behaviour programme (27). Using a group-/home-based format has been shown to be equally effective, and the cost savings are evident (26). Furthermore, we may have had lower costs using nursing consultations in the psycho-educative approach and we did not include the costs of housing, equipment and management. We found a lower cost of physiotherapy in the rehabilitation group. This could be explained by the fact that experimental physiotherapy is calculated into the total cost of rehabilitation in the rehabilitation group, whereas outpatient physiotherapy is calculated on its own. Another explanation could be that rehabilitation is preventive for further needs. We found the total attributable cost of the COPE-ICD trial to be -6,789 USD-PPP/-5,593 Euro-PPP in favour of the intervention. This cannot be explained by significantly lower numbers of admissions or length of stay, and therefore must be explained by more expensive treatment. The programme thus appears to result in a cost saving. None of the previous ICD rehabilitation trials have reported net savings.

Generalizability

External validity is high, since this population was included following the guidelines for ICD implantation from 2006. The baseline measures were mostly similar to findings from trials conducted in the USA and Europe (15, 28, 19). The use of blinded outcome assessment increased the validity of the data.

Study limitations

Study limitations include the fact that selection bias may exist, as we did not include patients if they were already included in other trials. Looking at the baseline measures it seems as though the randomization worked as there are comparable values. A slightly higher number of patients in the usual care group had a history of ischaemic heart disease and New York Heart Association Class (NYHA III) than in the rehabilitation group; however, no significant difference in 6MWT and VO_2 were seen between groups before the intervention occurred (3). The usual care group might have been contaminated by the information given during the project inclusion, suggesting that psycho-educational assistance and exercise training might be beneficial after ICD implantation. This information may have led to usual care patients seeking rehabilitation elsewhere. Collateral intervention occurred when some patients were offered cardiac rehabilitation at their local hospital, which may have reduced the effects of the experimental intervention, but resulted in conservative estimations of differences, by groups.

We used register-based follow-up information, which ensured close to complete follow-up.

Costs were calculated using average costs at a national level. Micro-costing based on accurate resource utilization is likely

to be more accurate and reliable. Use of DRG in pricing of hospitalizations may be inadequate in capturing the true benefit of the intervention, as a minimization in, for example, bed days will not be reflected in a lower overall DRG (4). Costing of the rehabilitation intervention only included variable costs and did not include capital costs, indicating an underestimation of the costs.

Clinical and research implications

We continue to see high readmission rates in this population and the beneficial effect of ICD-specific rehabilitation on mortality and ICD shock is still poorly investigated. Even though the "hard" endpoints, adverse events, did not seem to be affected this should be interpreted with caution due to low numbers and the explorative nature of these analyses.

However, we found that exercise training, in combination with psycho-educational consultations by a nurse, improves exercise capacity, general and mental health and seems to produce a cost saving over time. There are reasons to believe that this approach is beneficial in clinical practice in terms of quality of life and from a cost perspective. Larger multicentre trials designed with adverse events outcomes are needed to determine the effects on adverse events.

In conclusion, no difference in ICD shock, mortality or time to first admission was found between the groups. The total attributable cost of the intervention was -6,789 USD/-5,593 Euro in favour of the intervention.

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