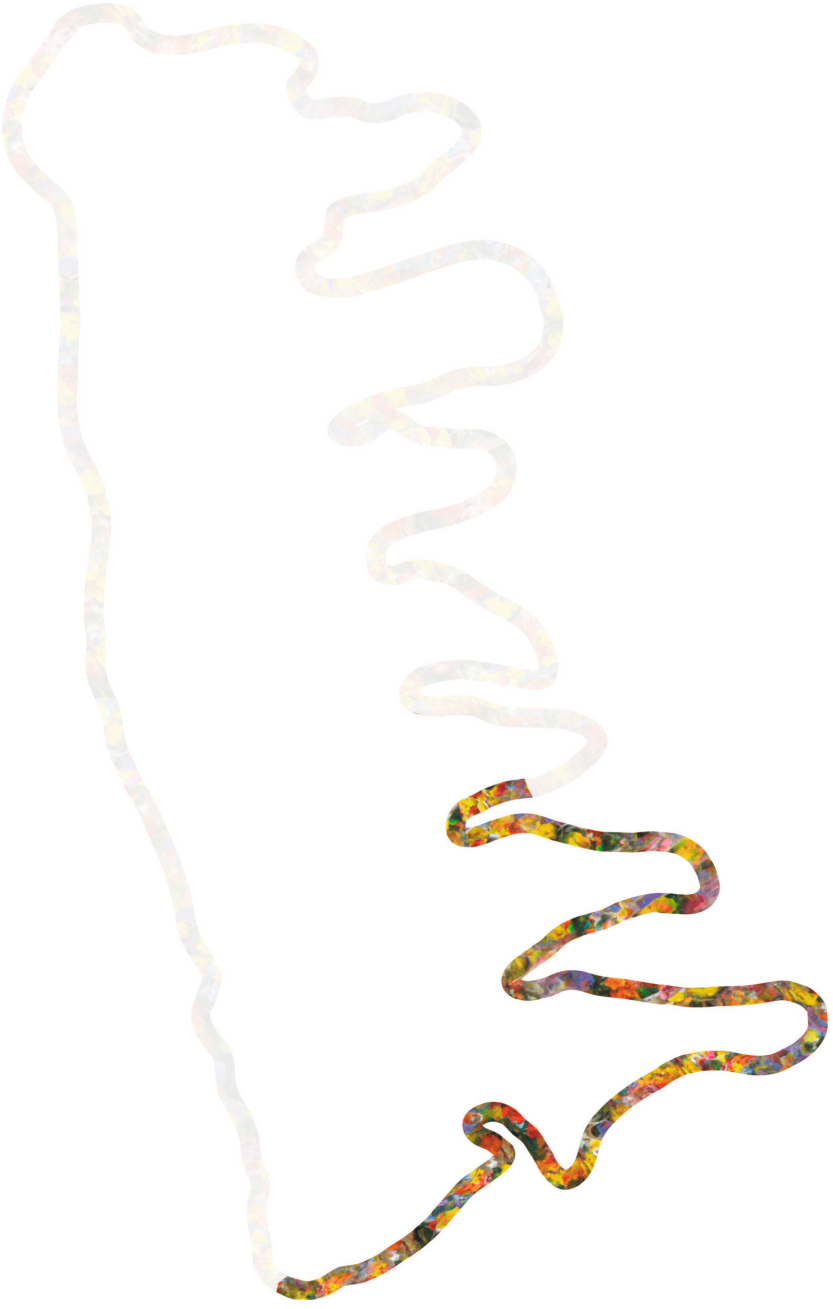
Outcome after anterior cervical discectomy: from inferential statistics to Machine Learning

Goedmakers, C.M.W.



Chapter 4

The Clinical Relevance of the Cervical Disc Prosthesis: Combining

Clinical Results of Two RCTs

Goedmakers CMW[1], Bartels RHMA[2], Donk RD[3], Arts MP[4], van Zwet EW[5], Vleggeert-Lankamp CLA[1]

Spine (Phila Pa 1976). 2022 Jan 1;47(1):67-75.

[1] Department of Neurosurgery, Leiden University Medical Center, Leiden, the Netherlands, [2] Department of Neurosurgery, Radboud University Medical Centre, Nijmegen, The Netherlands, [3] Department of Orthopaedics, Via Sana Clinics, Nijmegen, the Netherlands, [4] Department of Neurosurgery, Haaglanden Medical Center, The Hague, the Netherlands, [5] Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, the Netherlands

Abstract

Study Design

Retrospective analysis was performed on data from 251 patients that were included in two randomized, double-blinded clinical trials comparing clinical results of anterior cervical discectomy and arthroplasty (ACDA) to anterior cervical discectomy and fusion (ACDF), and anterior cervical discectomy (ACD), for single-level disc herniation.

Objective

This study aimed to investigate whether the ACDA procedure offers superior clinical results 2 years after surgery, to either ACDF or ACD without instrumentation, in the entire group of patients or in a particular subgroup of patients.

Summary of Background Data

The cervical disc prosthesis was introduced to provide superior clinical outcomes after ACD.

Methods

Neck Disability Index (NDI), and subscales of the 36-item short-form health survey (SF-36) and McGill pain score were collected at baseline, 1 year and 2 years after surgery. Reoperations and complications were also evaluated. A preliminary subgroup analysis was performed for age, disc height, body mass index (BMI), smoking, and sex.

Results

The NDI decreased comparably in all treatment arms to circa 50% of the baseline value and marginal mean NDI differences varied from 0.4 to 1.1 on a 100 point NDI scale, with confidence intervals never exceeding the 20-point minimal clinical important difference (MCID). Secondary outcome parameters showed comparable results. Preliminary subgroup analysis could not demonstrate clinically relevant differences in NDI between treatments after 2 years.

Conclusion

After combining data from two Randomized Controlled Trials it can be concluded that there is no clinical benefit for ACDA, when compared with ACDF or ACD 2 years after surgery. Preliminary subgroup analysis indicated outcomes were similar between treatment groups, and that no subgroup could be appointed that benefited more from either ACD, ACDF, or ACDA.

Introduction

Anterior cervical discectomy and fusion (ACDF) is the standard surgical treatment for patients suffering from radiculopathy due to a herniated disc, since first described by Smith, Robinson, Cloward, Dereymaeker and Mulier in the 1950s [1-3]. However, it is hypothesized that fusing the segments may increase the mechanical load on the adjacent segments and thus increase the incidence of adjacent segment disease [4, 5]. In order to simulate the mobile characteristics of a cervical disc, the cervical intervertebral disc prosthesis was introduced.

Following the introduction of the prosthesis the device has been the subject of several clinical and biomechanical studies. Trials comparing ACDF and prosthesis (anterior cervical discectomy and arthroplasty, ACDA) were widely performed but focused mainly on safety rather than superiority of the prosthesis [6-14]. Randomized Controlled Trials (RCTs) comparing ACDA to ACDF have been topic of debate, as the studies generally show a positive effect for the prosthesis, but are often non-blinded, industry-sponsored, and show small, not clinically relevant advantages in comparison to the golden standard ACDF [15].

Some years after the introduction of ACDF, and far before the introduction of the prosthesis, anterior cervical discectomy without instrumentation (anterior cervical discectomy, ACD) was first reported [16]. The induction of local kyphosis by ACD became the major argument to choose ACDF over ACD as the golden standard. Therefore most comparative studies focused on arthroplasty and ADCF, while ACD has not received that same amount of attention.

In this study we combined data from two RCTs, performed in two Academic hospitals in order to draw a strong conclusion on the alleged clinical superiority of ACDA. Both trials compare clinical outcomes for ACDA and ACDF, while adding a comparison to the less-studied alternative; ACD.

The two trials were designed to demonstrate the superiority of a cervical disc prosthesis, but were underpowered and individually showed no significant, nor clinically relevant advantage neither for ACDA over ACDF, nor over ACD [17, 18]. As a result of the larger sample size in this study, power can be improved and a preliminary subgroup analysis for age, disc height at baseline, BMI, smoking, and sex can be performed, according to the NECK trial protocol [19].

Materials and Methods

Design

Two prospective, randomized, double-blinded trials were conducted among patients with cervical radiculopathy due to single-level disc herniation. Both trials followed the CONSORT 2010 guidelines. Patients were randomly assigned into three groups ACDA, ACDF, or ACD. Written informed consent was obtained from all patients. Both study protocols obtained permission from the Medical Ethics Committee, and were published previously [19, 20].

Eligibility and Randomization

In order to match inclusion criteria patients had to be aged between 18 and 65 years old. Patients needed to present with radicular signs and symptoms in one or both arms (pain, paresthesia, or paresis in a specific nerve root distribution) due to a single level cervical intervertebral disc herniation, with or without an osteophyte in accordance with magnetic resonance imaging (MRI) findings. Patients with previous cervical surgery or absence of motion of the involved level, were excluded.

Both trials used a randomized, computer-aided design with variable block sizes to allocate stratified according to center in 1:1:1 ratio. The two trials both used a three arm, parallel group, superiority design, in which the ACDA group was the experimental group and the ACDF and ACD group were the control groups.

Interventions

All patients included in either one of the trials underwent standard anterior cervical discectomy with bilateral decompression of the nerve roots. After the disc was removed the intervertebral space was either left unfilled (ACD), a prosthesis was placed (ACDA), or a cage was inserted (ACDF). The NECK trial studied activ®C flat artificial cervical disc (Aesculap AG, Tuttlingen, Germany), the Pro-con trial the Bryan® disc prosthesis (Medtronic, Memphis, TN). In both trials fusion was established using a PEEK cage without plate, filled with autologous bone or bone substitute.

In each trial the prostheses were placed by a maximum of four different senior spine surgeons, that were trained to implant the prostheses. In the Procon trial patients allocated to ACDA were prescribed Meloxicam for 2 weeks to prevent heterotopic ossification. Postoperatively all patients were encouraged to mobilize as soon as possible. No collars were prescribed.

Outcomes

In this study outcomes were analyzed at baseline, one year and two years after surgery. The primary outcome measure is the Neck Disability Index (NDI) [21-24]. The NDI is a 10-item questionnaire on three different aspects; pain intensity, daily work related activities, and non-work related activities. The 50 points score was converted to a 100 points scale. The NDI is a modification of the Oswestry Low Back Pain Questionnaire and Secondary outcome measures were the physical-component score (PCS) and the mental-component score (MCS) of the 36-item short-form health survey (SF-36) and the pain rating index-total (PRI-T) and the number of words chosen-total (NWC-T) of the McGill pain questionnaire Dutch language version (MPQ-DLV). Additionally, data on complications and reoperations were summarized.

The SF-36 is a generic health status questionnaire, validated in surgical studies on spinal column pathology that can easily be filled out at home [25-27]. The questionnaire consists of 36 items on physical and social status of the patient subdivided in subscales. The questions are scored on a scale of 0 (worst health) to 100 (ideal health) in this questionnaire. The PCS and MCS are derived from the SF-36 and are summary scores for respectively the physical quality of life and the mental

quality of life. The PCS and MCS range from 0 to 100, with higher scores representing better self-reported health.

The MPQ-DLV includes several domains, one of them is a questionnaire that assesses pain intensity using a list of adjectives from which patients can choose words to describe their pain. The number of chosen adjectives in the sensory, affective and evaluative subscales is counted which gives the "number of words chosen-total" (NWC-T), values of the NWC-T in this study ranged from 0 to 20. Also the sum of the ranks belonging to each adjective gives the "pain rating index-total" (PRI-T) with values in this study ranging from 0 to 56. In this article we refer to these scores as the "MPQ-PRI" and the "MPQ-NWC."

Sample Size

Both studies had a superiority design, in which the superiority assumption was assumed; with the hypothesis that the average NDI 2 years after ACDA surgery, would be superior (lower) than the average NDI in patients that underwent ACDF or ACD.

The Procon trial planned for a sample size of 243 patients, while the NECK trial calculated a required sample size of 166 patients, based on previous literature [4, 28]. Both studies did not achieve the aimed sample size and were therefore underpowered. After combining data from both studies, a total sample size of 251 patients was achieved for this analysis, and effect sizes could be estimated with narrow confidence intervals.

Previous publications have used several different methods to calculate the minimal clinical important difference (MCID) for NDI [24, 29-32]. Averaging the different estimates from literature, a difference of 20 points on a 100 point scale in NDI was considered a valid MCID. Likewise, the MCID for PCS and MCS differs in literature [30-32]. Averaging the reported values gives an approximated MCID for PCS and MCS of six, out of the total score of 100. Substantial evidence about the MCIDs for the MPQ-DLV is lacking. The importance of incorporating clinical relevance of results in articles is discussed previously [15, 33].

Statistical Analysis

General Analysis

IBM SPSS software, version 22.0, was used for all statistical analysis. Groups were compared based on an intention-to-treat analysis. Differences between the three groups at baseline were tested using the chi-squared test for categorical values and the ANOVA test for continuous values. Numerical data were represented by mean value ± standard deviation (SD).

To account for the correlation between repeated measurements of the same individual, generalized estimating equations (GEE) were used. The estimated marginal means estimates table handles missing data through mean at univariate pooling. In this model the follow-up moment, the treatment group, and the study type were used to explain the dependent variables (NDI, MPQ-PRI, MPQ-NWC, PCS, and MCS). We used an exchangeable correlation matrix structure and

Wal test. The GEE approach is not a full likelihood approach. Therefore, likelihood ratio test and score test cannot be used. However, (generalized) Wald tests are available and were therefore used.

Subgroup Analysis

Cut-off values for the subgroup-analyses were predefined in the NECK trial protocol, which was established in close cooperation with the statistician [19]. The explorative subgroup analysis was only performed for the primary outcome measure; NDI.

Results

Between October 5, 2003 and June 10, 2010 the Procon trial included 142 patients, and between October 2010 and July 2014 the NECK trial included 109 eligible patients. Data were retrospectively combined and analyzed, creating a data-set with individual patient data on 251 patients at baseline. The mean age of patients at the moment of operation was 45.0 (SD ± 7.5) and 51% was female. Baseline characteristics were comparable between treatment arms (Table 1). Two years after surgery, primary outcome data were available on 159 patients, corresponding to a 63% compliance rate.

Table 1. Patient demographics

	ACD	ACDF	ACDA	Total
Number (n)	83	83	85	251
Age (yr)	45.1 ± 6.6	44.9 ± 8.3	45.1 ± 7.8	45.0 ± 7.5
Gender (F/M)	41/42	44/39	44/41	129/122
Smoking (Y/N)	33/50	39/43	41/44	113/137
BMI	26.0 ± 3.8	26.5 ± 4.7	26.8 ± 4.1	26.5 ± 4.2
Disc height (mm)	5.7 ± 1.1	5.6 ± 1.4	6.0 ± 1.3	5.8 ± 1.3
NDI	39.3 ± 15.1	39.0 ± 14.1	41.1 ± 16.5	39.8 ± 15.2

Baseline characteristics of included patients allocated to anterior cervical discectomy without any implant (ACD), anterior cervical discectomy with fusion by cage (ACDF) or anterior cervical discectomy with arthroplasty (ACDA) All characteristics were similar between groups without reaching statistical significance for any difference. Numerical data represented as mean ± SD. ACD indicates anterior cervical discectomy; ACDA, anterior cervical discectomy and arthroplasty; ACDF, anterior cervical discectomy and fusion; NDI, Neck Disability Index

Primary Outcome

The NDI decreased comparably in all treatment arms from 39.58 to 41.85 preoperatively to 14.62 ± 3.1 (ACD), 22.5 ± 3.6 (ACDF), and 22.7 ± 4.3 (ACDA) after 2 years (Table 2). NDI differences in marginal means between groups after 2 years were 1.113 (CI −4.77–6.99; ACDA vs. ACD), 0.424 (CI −5.79–6.64 ACDA vs. ACDF), and 0.688 (CI −4.62–5.99; ACDF vs. ACD), on a 100

point NDI scale (Table 3). In all three comparisons the difference in marginal means between the groups and corresponding confidence intervals never exceeded the MCID for NDI of 20 (Figure 1).

Table 2. Summarizing table for primary and secondary outcomes

	Baseline		1 year FU		2 year FU	
	Mean	**Std. Error**	**Mean**	**Std. Error**	**Mean**	**Std. Error**
NDI						
ACD	39.58	1.56	16.48	1.84	14.62	1.76
ACDF	39.60	1.56	15.75	1.90	15.30	2.05
ACDA	41.85	1.74	14.39	1.81	15.73	2.43
MPQ-NWC						
ACD	10.22	0.49	5.80	0.61	6.33	0.64
ACDF	9.44	0.50	6.61	0.73	5.11	0.65
ACDA	8.80	0.47	5.82	0.60	5.57	0.74
MPQ-PRI						
ACD	18.16	1.03	8.53	0.98	9.64	1.21
ACDF	16.72	1.08	10.06	1.18	7.71	1.04
ACDA	16.10	1.14	8.53	1.15	8.30	1.33
PCS						
ACD	35.03	0.84	48.16	1.19	47.81	1.43
ACDF	36.83	0.77	48.96	1.12	49.07	1.14
ACDA	35.69	0.75	48.27	₴1.10	49.37	1.40
MCS						
ACD	46.30	1.32	52.07	1.21	49.79	1.62
ACDF	44.51	1.41	51.84	1.30	52.67	1.22
ACDA	44.38	1.40	50.70	1.13	49.85	1.30

Estimated marginal means values of NDI, MPQ-NWC, MPQ-PRI, PCS, MCS at baseline, after one year and after two years, with Standard Errors. Scores were computed using Generalized Estimated Equations to account for correlation between repeated measurements, missing values and study hospital.
MPQ=McGill Pain Questionnaire, NWC=Total number of words chosen in the sensory, affective and evaluative subscales, PRI=Pain Rating Index, PCS=Physical Component Summary score, MCS=Mental Component Summary score.

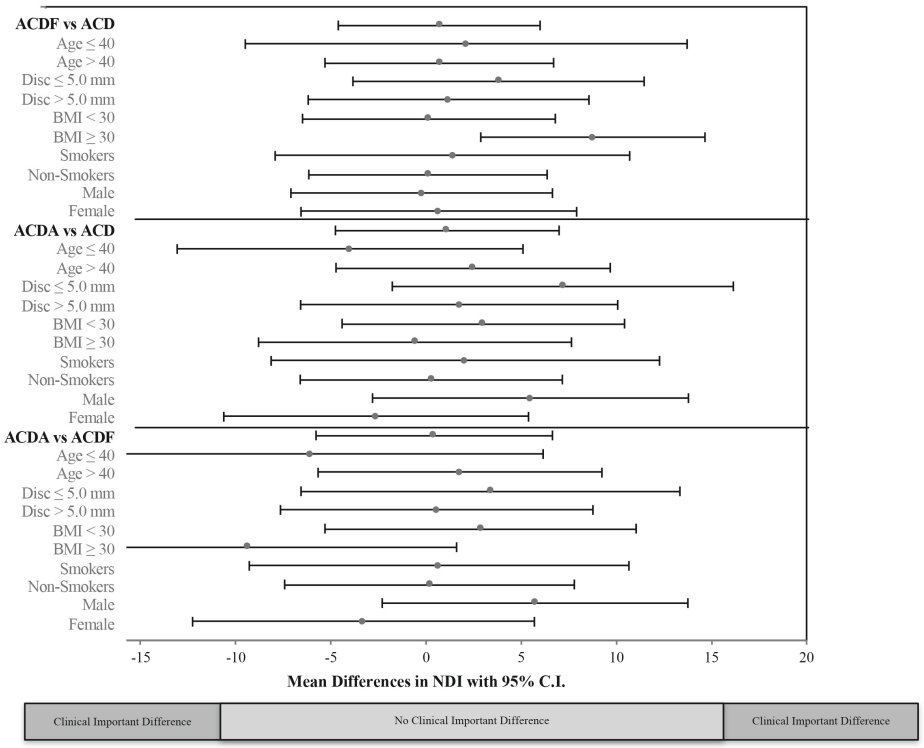


Figure 1. Mean differences in NDI for all subgroups per treatment group

Summarizing figure with mean differences in NDI after 2 years, based on the differences between marginal mean values with minimal and maximal mean differences (95%) for all treatment groups and subgroups. NDI indicates Neck Disability Index.

Secondary Outcome

PCS and MCS showed an increase in quality of life, comparable between the treatment groups with small standard errors (Table 2). Values increased from 35.03 to 36.83 preoperatively to 47.81 ± 1.43 (ACD), 49.07 ± 1.14 (ACDF), and 49.37 ± 1.40 (ACDA) after 2 years for PCS. For MCS values increased from 44.38 to 46.30 preoperatively to 49.79 ± 1.62 (ACD), 52.67 ± 1.22 (ACDF), and 49.85 ± 1.30 (ACDA) after 2 years. The differences in marginal means were small and not significantly different between the three groups, neither after 1 nor 2 years postoperatively (Table 3). The MCID for PCS and MCS of six, out of the total score of 100, is not reached in any of the comparisons.

Estimated marginal means for MPQ-NWC and MPQ-PRI decreased comparably (Table 2). Values decrease from 8.80 to 10.2 preoperatively to 6.33 ± 0.64 (ACD), to 5.11 ± 0.65 (ACDF), and to 5.57 ± 0.74 (ACDA) after 2 years for MPQ-NWC. For MPQ-PRI values decline from 16.10 to 18.16 preoperatively to 9.64 ± 1.21 (ACD), to 7.71 ± 1.04 (ACDF), and to 8.30 ± 1.33 (ACDA) after 2 years.

Table 3. Mean differences for the treatment groups after two years for all outcome variables

	Mean difference	95% CI lower bound	95% CI upper bound	
ACDF vs ACD				
NDI	0.688	-4.62	5.99	p = 0.799
MPQ-NWC	-1.219	-3.00	0.561	P = 0.180
MPQ-PRI	-1.935	-5.06	1.19	P = 0.225
PCS	1.260	-2.33	4.85	P = 0.492
MCS	2.886	-1.09	6.86	P = 0.154
ACDA vs ACD				
NDI	1.113	-4.77	6.99	p = 0.711
MPQ-NWC	-0.755	-2.67	1.16	P = 0.440
MPQ-PRI	-1.34	-4.85	2.18	P = 0.455
PCS	1.561	-2.35	5.47	P = 0.434
MCS	0.060	-4.02	4.14	P = 0.977
ACDA vs ACDF				
NDI	0.424	-5.79	6.64	p = 0.894
MPQ-NWC	0.464	-1.47	2.39	P = 0.638
MPQ-PRI	0.596	-2.71	3.90	P = 0.724
PCS	0.301	-3.23	3.83	P = 0.867
MCS	-1.785	-6.33	0.67	P = 0.113

The difference in estimated marginal means between treatment groups for NDI, MPQ-NWC, MPQ-PRI, PCS and MCS. Scores were computed using Generalized Estimated Equations to account for correlation between repeated measurements, missing values and study hospital.
MPQ=McGill Pain Questionnaire, NWC=Total number of words chosen in the sensory, affective and evaluative subscales, PRI=Pain Rating Index, PCS=Physical Component Summary score, MCS=Mental Component Summary score.

Subgroup Analysis

Preliminary subgroup analysis on NDI for age, disc height at baseline, BMI, smoking, and sex confirm small differences between treatments, with confidence intervals never exceeding the 20-point difference of the MCID for NDI (Table 4, Figure 1).

In the subgroup of patients with higher BMI (≥30), disability was significantly higher 2 years after surgery in patients that underwent ACDF when compared with both ACDA, and ACD (Table 4, Figure 1). There were no other statistically significant differences found in the subgroup analysis. In general, smokers report higher NDI scores after 2 years, compared with non-smokers and, females reported higher NDI scores than males (Table 4). Trends can be observed, however the trial was never powered for a subgroup analysis and caution should therefore be taken while interpreting the results.

Table 4. Mean differences in NDI between treatment groups for all subgroups after two years

	Mean difference	95% CI lower	95% CI upper	P-value
ACDF vs ACD	**0.688**	**-4.62**	**5.99**	**p = 0.799**
Age ≤ 40	2.103	-9.51	13.72	p = 0.723
Age > 40	0.689	-5.32	6.70	p = 0.822
Disc ≤ 5.0 mm	3.805	-3.85	11.46	p = 0.330
Disc > 5.0 mm	1.181	-6.20	8.56	p = 0.754
BMI < 30	0.148	-6.50	6.79	p = 0.965
BMI ≥ 30	8.764	2.87	14.66	p = 0.004
Smokers	1.381	-7.94	10.70	p = 0.772
Non-smokers	0.092	-6.17	6.36	p = 0.977
Male	-0.238	-7.11	6.64	p = 0.946
Female	0.666	-6.58	7.91	p = 0.857
ACDA vs ACD	**1.113**	**-4.77**	**6.99**	**p = 0.711**
Age ≤ 40	-4.000	-13.09	5.09	p = 0.388
Age > 40	2.470	-4.74	9.68	p = 0.502
Disc ≤ 5.0 mm	7.187	-1.78	16.15	p = 0.116
Disc > 5.0 mm	1.736	-6.60	10.07	p = 0.683
BMI < 30	3.005	-4.42	10.43	p = 0.427
BMI ≥ 30	-0.584	-8.81	7.64	p = 0.889
Smokers	2.060	-8.15	12.27	p = 0.693
Non-smokers	0.266	-6.62	7.16	p = 0.940
Male	5.486	-2.82	13.79	p = 0.195
Female	-2.629	-10.64	5.38	p = 0.520
ACDA vs ACDF	**0.424**	**-5.79**	**6.64**	**p = 0.894**
Age ≤ 40	-6.103	-18.36	6.15	p = 0.329
Age > 40	1.781	-5.68	9.24	p = 0.640
Disc ≤ 5.0 mm	3.382	-6.58	13.34	p = 0.506
Disc > 5.0 mm	0.555	-7.66	8.77	p = 0.895
BMI < 30	2.86	-5.32	11.04	p = 0.493
BMI ≥ 30	-9.35	-17.10	1.60	p = 0.018
Smokers	0.679	-9.30	10.66	p = 0.894
Non-smokers	0.174	-7.44	7.79	p = 0.964
Male	5.724	-2.31	13.76	p = 0.163
Female	-3.30	-12.28	5.69	p = 0.472

The difference in estimated marginal mean NDI between groups after two years. Scores were computed using Generalized Estimated Equations to account for correlation between repeated measurements, missing values and study hospital.

Table 5. Complications & Re-operations

Complications	**ACD**			**ACDF**			**ACDA**		
	NECK	Procon	Combined	NECK	Procon	Combined	NECK	Procon	Combined
Number of patients	38	45	83	36	47	83	35	50	85
Superficial wound infection	0 (0)	0 (0)	0 (0)	1 (2.8)	1 (2.1)	2 (2.4)	0 (0)	0 (0)	0 (0)
Hoarseness	3 (7.9)	3 (6.7)	6 (7.2)	2 (5.6)	1 (2.1)	3 (3.6)	5 (14.3)	0 (0)	5 (5.9)
Dysphagia	3 (7.9)	1 (2.2)	4 (4.8)	4 (11.1)	4 (8.5)	8 (9.6)	6 (17.1)	2 (4.0)	8 (9.4)
Postoperative hemorrhage	0 (0)	1 (2.2)	1 (1.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Subcutaneous hemorrhage	1 (2.6)	0 (0)	1 (1.2)	1	0 (0)	1 (1.2)	2 (5.7)	0 (0)	2 (2.4)
Total	7 (18.4)	5 (11.1)	12 (14.5)	8 (22.2)	6 (12.8)	14 (16.7)	13 (37.1)	2 (4.0)	15 (17.6)

Re-operations	**ACD**			**ACDF**			**ACDA**		
	NECK	Procon	Combined	NECK	Procon	Combined	NECK	Procon	Combined
Surgery for adjacent segment disease	2 [e] (5.3)	3 (6.7)	5 (6.0)	3 (8.3)	5 (10.6)	8 (9.6)	2 [e] (5.7)	0 (0)	2 (2.4)
Surgery for recurrent compression at index level [a]	1 [b] (2.6)	1 [c] (2.2)	2 (2.4)	0 (0)	1 (2.1)	1 (1.2)	1 (2.9)	1 (2.0)	2 (2.4)
Posterior surgery	0	1	1	0	1	1	0	1 [d]	1
Anterior surgery	1	1	2	0	0	0	1	0	1
Total	3	4	7 (8.4)	3	6	9 (10.8)	3	1	4 (4.7)

Data represented as number (% of group). Urinary tract infection, pulmonary infection, deep venous thrombosis, pulmonary embolism or deep wound infection did not occur. Re-operations for recurrent signs and symptoms due to nerve root compression at index level or adjacent segment related to treatment group. Data represented as number, (% of group). Reoperations are not significantly different between the treatment groups.

[a] Surgery for recurrent compression at index level was subdivided under 'anterior' and 'posterior'.

[b] One patient was re-operated at both index level and adjacent level and was therefore counted double.

[c] One patient was also operated anteriorly because of insufficient result of the first posterior re-exploration.

[d] One patient visited the outpatient clinical for recurrent signs and symptoms before completing the NDI questionnaire. This crossed the radiological examinations. after which she was offered surgical therapy for recurred stenosis at the index level.

[e] Two patients had a herniated disc at the adjacent level upon randomization. which did not give complaints radiculopathy at time of randomization. However. after surgery complaints of the adjacent level started.

Complications and Reoperations

Forty one out of the 251 patients experienced a complication after surgery, not related to recurrent signs or symptoms of radiculopathy at index or the adjacent level. In 12 (14.5%) in the ACD group, 14 (16.7%) in the ACDF group and 15 (17.6%) patients in the ACDA group occurred a complication (Table 5). The number of complications was not statistically significantly different between the treatment groups (P = 0.844).

Fifteen out of 251 patients were reoperated due to recurrent signs or symptoms of radiculopathy at the adjacent level, five (6.0%) in the ACD group, eight (9.6%) in the ACDF group, and four (4.7%) in the ACDA group. Five patients were reoperated at the index level, two in the ACD group, one in the ACDF group, and two in the ACDA group. The number of reoperations did not differ statistically significant between groups, neither for index level (P = 0.334), nor for the adjacent segment reoperations (P = 0.138) (Table 5).

Discussion

This study combined two randomized, double-blinded clinical trials on anterior decompression in cervical radiculopathy and demonstrated that at two year follow up a clinical advantage for the cervical disc prosthesis is absent, when compared to the golden standard ACDF. In contrast to what is globally hypothesized by many spinal surgeons, Superior outcome after ACDA could not even be confirmed when ACDA was compared to ACD. Additionally, preliminary subgroup analysis could not indicate a certain type of patient that would benefit more from receiving the prosthesis two years after surgery.

The rationale for placing an intervertebral device is that the original height of the removed disc should be restored in order to keep the neuroforamen at its original height. However, the small differences and narrow confidence intervals found in this study suggest that placement of an intervertebral device might not be not essential, for single level discectomy. This conclusion is in agreement with the results presented in the Cochrane review on comparison of interbody fusion techniques in the treatment of cervical radiculopathy, and two other systematic reviews on the topic [34-36]. Likewise, a ten-year follow-up study of 102 patients being subjected to discectomy alone (ACD) demonstrated satisfactory results [37].

A major strength of this study is that individual patient data from two identical RCTs was combined, comparing ACDA and ACDF, while adding a comparison to the less-studied alternative; ACD. Combining RCT results in this manner is financially sustainable, facilitates the optimal use of resources and experience of each center and is very similar to the concept of 'practical clinical trials' as described in JAMA (2003) [38]. Additionally, the increase in sample size improves statistical power. Another strength is the incorporation of clinically relevant outcome measures, as too often trials report on small treatment differences that are not clinically relevant to the patient.

These results should however be seen in light of some limitations. The follow-up period of two years is a limitation to this study. For the ambivalence surrounding ACD is not only the short-

term clinical outcome, but rather the long-term effects of local kyphosis, adjacent segment disease, recurrent cervical radiculopathy and neck pain. It is possible that adjacent level disease will occur after the period of two years and that this would have subsequent clinical outcome effects. Even though the Procon trial nine-year follow-up results do not demonstrate this tendency, we want to stress the importance of long-term outcome assessment when ASD is concerned [17]. When segmental angulation was investigated in the NECK trial, of the patients with a kyphotic cervical curvature at baseline, only 1 patient remained kyphotic; the other 6 patients recovered to a straight or lordotic spine during two years follow-up. The number of patients with a kyphotic spine was too small to correlate this to clinical data [18]. Nevertheless, conclusions drawn after two years have to be interpreted cautiously, and five-year follow-up results, accompanied by radiological evaluation of particularly the ACD group, should be awaited before the absence of an intervertebral device can be advocated as a solid alternative to fusion.

One might argue that another limitation to this study is the use of different prostheses; ActivC® and Bryan®. There is however no literature available that proves that either device functions significantly better or worse than the other, in terms of clinical outcomes after surgery. This supports our belief that both prostheses can be validly compared to each other.

Another limitation is the combined compliance rate of 63% after two years. With 159 patients having a complete follow-up record after two years and the needed sample size to achieve power calculated at 166, the study is underpowered. Although, drop-out rates are comparable between treatments groups and the found differences are minimal with narrow confidence intervals, it should be noted that 7 additional patients would have been needed at this follow-up moment to achieve the sample size number from the pre hoc power calculation.

It should be noted that MCID is a topic of discussion and the variable ways of calculating MCID values contribute to the difference in values reported, of which anchor and distribution-based methods are the most widely used. In determining the values for MCID we attempted to base the used values on different publications, each using different methods to approximate MCID [23, 24, 30, 32, 39].

Results from this study demonstrate that there is no clinical benefit for ACDA, when compared to ACDF or ACD two years after surgery. The small differences with narrow confidence intervals found in this study, especially for the ACDA vs. ACD and ACDF vs. ACD comparison, are surprising and suggest that this method should not be ruled out in future comparative research.

Findings in this study can be generalized to a patient population undergoing single level surgery, with a wide ranging age, exclusively suffering from radiculopathy. The five-year and ten-year clinical and radiological results of this study should provide additional information about long-term effects of the three treatment strategies.

References

1. Robinson R. Anterolateral disc removal and interbody fusion for cervical disc syndrome. Bull Johns Hopkins Hosp. 1955;96:223-4.
2. Cloward RB. The anterior approach for removal of ruptured cervical disks. J Neurosurg. 1958;15(6):602-17.
3. Dereymaeker A, Mulier J. [Vertebral fusion by a ventral approach in cervical intervertebral disk disorders]. Rev Neurol (Paris). 1958;99(6):597-616.
4. Robertson JT, Papadopoulos SM, Traynelis VC. Assessment of adjacent-segment disease in patients treated with cervical fusion or arthroplasty: a prospective 2-year study. Journal of Neurosurgery: Spine. 2005;3(6):417-23.
5. Eck JC, Humphreys SC, Lim TH, Jeong ST, Kim JG, Hodges SD, et al. Biomechanical study on the effect of cervical spine fusion on adjacent-level intradiscal pressure and segmental motion. SPINE. 2002;27(22):2431-4.
6. Hou Y, Nie L, Pan X, Si M, Han Y, Li J, et al. Effectiveness and safety of Mobi-C for treatment of single-level cervical disc spondylosis A RANDOMISED CONTROL TRIAL WITH A MINIMUM OF FIVE YEARS OF FOLLOW-UP. BONE & JOINT JOURNAL. 2016;98B(6):829-33.
7. Janssen ME, Zigler JE, Spivak JM, Delamarter RB, Darden BV, Kopjar B. ProDisc-C Total Disc Replacement Versus Anterior Cervical Discectomy and Fusion for Single-Level Symptomatic Cervical Disc Disease Seven-Year Follow-up of the Prospective Randomized US Food and Drug Administration Investigational Device Exemption Study. JOURNAL OF BONE AND JOINT SURGERY-AMERICAN VOLUME. 2015;97A(21):1738-47.
8. Loumeau TP, Darden BV, Kesman TJ, Odum SM, Van Doren BA, Laxer EB, et al. A RCT comparing 7-year clinical outcomes of one level symptomatic cervical disc disease (SCDD) following ProDisc-C total disc arthroplasty (TDA) versus anterior cervical discectomy and fusion (ACDF). EUROPEAN SPINE JOURNAL. 2016;25(7):2263-70.
9. Murrey D, Janssen M, Delamarter R, Goldstein J, Zigler J, Tay B, et al. Results of the prospective, randomized, controlled multicenter Food and Drug Administration investigational, device exemption study of the ProDisc-C total disc replacement versus anterior discectomy and fusion for the treatment of 1-level symptomatic cervical disc disease. SPINE JOURNAL. 2009;9(4):275-86.
10. Nabhan A, Ahlhelm F, Shariat K, Pitzen T, Steimer O, Steudel WI, et al. The ProDisc-C prothesis - Clinical and radiological experience 1 year after surgery. SPINE. 2007;32(18):1935-41.
11. Nabhan A, Steudel WI, Nabhan A, Pape D, Ishak B. Segmental kinematics and adjacent level degeneration following disc replacement versus fusion: RCT with three years of follow-up. Journal of long-term effects of medical implants. 2007;17(3):229-36.
12. Park JH, Roh KH, Cho JY, Ra YS, Rhim SC, Noh SW. Comparative Analysis of Cervical Arthroplasty Using Mobi-C (R) and Anterior Cervical Discectomy and Husion Using the Solis (R)-Cage. JOURNAL OF KOREAN NEUROSURGICAL SOCIETY. 2008;44(4):217-21.
13. Sala V, Lisi C, Di Natali G, Zanellato S, Dall'Angelo A, Tinelli C, et al. Functional and quality of life evaluation after single level cervical discectomy and fusion or cervical artificial disc replacement. GIORNALE ITALIANO DI MEDICINA DEL LAVORO ED ERGONOMIA. 2015;37(4):239-44.

14. Zhang HX, Shao YD, Chen Y, Hou Y, Cheng L, Si M, et al. A prospective, randomised, controlled multicentre study comparing cervical disc replacement with anterior cervical decompression and fusion. INTERNATIONAL ORTHOPAEDICS. 2014;38(12):2533-41.
15. Goedmakers CM, Janssen T, Yang X, Arts MP, Bartels RH, Vleggeert-Lankamp CL. Cervical radiculopathy: is a prosthesis preferred over fusion surgery? A systematic review. European Spine Journal. 2020;29:2640-54.
16. Hirsch C. Cervical Disk Rupture: Diagnosis and Therapy. Acta Orthopaedica Scandinavica. 1961;30(1-4):172-86.
17. Donk RD, Verbeek ALM, Verhagen WIM, Groenewoud H, Hosman AJF, Bartels R. What's the best surgical treatment for patients with cervical radiculopathy due to single-level degenerative disease? A randomized controlled trial. PLOS ONE. 2017;12(8).
18. Vleggeert-Lankamp CL, Janssen TM, van Zwet E, Goedmakers CM, Bosscher L, Peul W, et al. The NECK trial: effectiveness of anterior cervical discectomy with or without interbody fusion and arthroplasty in the treatment of cervical disc herniation; a double-blinded randomized controlled trial. The Spine Journal. 2019;19(6):965-75.
19. Arts MP, Brand R, van den Akker E, Koes BW, Peul WC. The NEtherlands Cervical Kinematics (NECK) Trial. Cost-effectiveness of anterior cervical discectomy with or without interbody fusion and arthroplasty in the treatment of cervical disc herniation; a double-blind randomised multicenter study. BMC Musculoskelet Disord. 2010.
20. Bartels R, Donk R, van der Wilt GJ, Grotenhuis JA, Venderink D. Design of the PROCON trial: a prospective, randomized multi-center study comparing cervical anterior discectomy without fusion, with fusion or with arthroplasty. BMC MUSCULOSKELETAL DISORDERS. 2006;7.
21. Vernon H, Mior S. The Neck Disability Index: a study of reliability and validity. J Manipulative Physiol Ther. 1991;14(7):409-15.
22. Pietrobon B, Coeytaux RB, Carey TS, Richardson WJ, DeVellis RF. Standard scales for measurement of functional outcome for cervical pain or dysfunction - A systematic review. SPINE. 2002;27(5):515-22.
23. Vos CJ, Verhagen AP, Koes BW. Reliability and responsiveness of the Dutch version of the Neck Disability Index in patients with acute neck pain in general practice. Eur Spine J. 2006;15(11):1729-36.
24. Young IA, Cleland JA, Michener LA, Brown C. Reliability, Construct Validity, and Responsiveness of the Neck Disability Index, Patient-Specific Functional Scale, and Numeric Pain Rating Scale in Patients with Cervical Radiculopathy. American Journal of Physical Medicine & Rehabilitation. 2010;89(10).
25. Ware JE, Sherbourne CD. THE MOS 36-ITEM SHORT-FORM HEALTH SURVEY (SF-36) .1. CONCEPTUAL-FRAMEWORK AND ITEM SELECTION. MEDICAL CARE. 1992;30(6):473-83.
26. Brazier JE, Harper R, Jones N, O'cathain A, Thomas K, Usherwood T, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. British medical journal. 1992;305(6846):160-4.
27. Stansfeld S, Roberts R, Foot S. Assessing the validity of the SF-36 General Health Survey. Quality of Life Research. 1997;6.
28. Bartels R, Donk R, Verbeek ALM. No Justification for Cervical Disk Prostheses in Clinical Practice: A Meta-Analysis of Randomized Controlled Trials. NEUROSURGERY. 2010;66(6):1153-60.
29. Young BA, Walker MJ, Strunce JB, Boyles RE, Whitman JM, Childs JD. Responsiveness of the Neck Disability Index in patients with mechanical neck disorders. The Spine Journal. 2009;9(10):802-8.
30. Auffinger BM, Lall RR, Dahdaleh NS, Wong AP, Lam SK, Koski T, et al. Measuring surgical outcomes in cervical spondylotic myelopathy patients undergoing anterior cervical discectomy and fusion: assessment of minimum clinically important difference. PLoS One. 2013;8(6):e67408.

31. Cleland JA, Childs JA, Whitman JM. Psychometric properties of the neck disability index and numeric pain rating scale in patients with mechanical neck pain. ARCHIVES OF PHYSICAL MEDICINE AND REHABILITATION. 2008;89(1):69-74.

32. Parker SL, Godil SS, Shah DN, Mendenhall SK, McGirt MJ. Assessment of the minimum clinically important difference in pain, disability, and quality of life after anterior cervical discectomy and fusion Clinical article. JOURNAL OF NEUROSURGERY-SPINE. 2013;18(2):154-60.

33. Bartels R, Donk RD, Verhagen WIM, Hosman AJF, Verbeek ALM. Reporting the results of meta-analyses: a plea for incorporating clinical relevance referring to an example. SPINE JOURNAL. 2017;17(11):1625-32.

34. Jacobs W, Willems PC, Kruyt M, van Limbeek J, Anderson PG, Pavlov P, et al. Systematic Review of Anterior Interbody Fusion Techniques for Single- and Double-Level Cervical Degenerative Disc Disease. Spine. 2011;36(14).

35. Matz PG, Ryken TC, Groff MW, Vresilovic EJ, Anderson PA, Heary RF, et al. Techniques for anterior cervical decompression for radiculopathy. Journal of Neurosurgery: Spine SPI. 2009;11(2):183-97.

36. van Middelkoop M, Rubinstein SM, Ostelo R, van Tulder MW, Peul W, Koes BW, et al. No additional value of fusion techniques on anterior discectomy for neck pain: A systematic review. PAIN. 2012;153(11).

37. Nandoe Tewarie RDS, Bartels RHMA, Peul WC. Long-term outcome after anterior cervical discectomy without fusion. European Spine Journal. 2007;16(9):1411-6.

38. Tunis SR, Stryer DB, Clancy CM. Practical Clinical TrialsIncreasing the Value of Clinical Research for Decision Making in Clinical and Health Policy. JAMA. 2003;290(12):1624-32.

39. Cook CE. Clinimetrics Corner: The Minimal Clinically Important Change Score (MCID): A Necessary Pretense. JOURNAL OF MANUAL & MANIPULATIVE THERAPY. 2008;16(4):82E-3E.