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Citation

Goedmakers, C. M. W., Bartels, R. H. M. A., Donk, R. D., Arts, M. P., Zwet, E. W. van, & Vleggeert-Lankamp, C. L. A. (2022). The clinical relevance of the cervical disc prosthesis combining clinical results of two RCTs. *Spine*, 47(1), 67-75. doi:10.1097/BRS.0000000000004113

Version: Publisher's Version

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Note: To cite this publication please use the final published version (if applicable).

CERVICAL SPINE

The Clinical Relevance of the Cervical Disc Prosthesis

Combining Clinical Results of Two RCTs

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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.

Key words: arthroplasty, cervical discectomy, cervical radiculopathy, cervical spine, disc herniation, fusion surgery, neck disability index, prosthesis, radicular pain, subgroup analysis.

Level of Evidence: 1
Spine 2022;47:67–75

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, Derymaecker 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

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Acknowledgment date: January 6, 2021. First revision date: March 2, 2021. Second revision date: April 7, 2021. Acceptance date: April 8, 2021.

The device(s)/drug(s) is/are FDA-approved or approved by corresponding national agency for this indication.

The NECK trial was sponsored by Braun Medical. The Department of Neurosurgery, Leiden University Medical Center took over funding responsibilities. The Procon trial was sponsored by the Department of Neurosurgery of the Radboud University Medical Center Nijmegen, the Netherlands. Relevant financial activities outside the submitted work: board membership, grants, royalties, payment for lecture.

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DOI: 10.1097/BRS.0000000000004113

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 ACDF, 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

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.^{25–27} that can easily be filled out at home. 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.”

In this study outcomes were analyzed at baseline, one year and two years after surgery.

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

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 \pm 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 Wald 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.

IBM SPSS software, version 22.0, was used for all statistical analysis.

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 dataset with individual patient data on 251 patients at baseline.

The mean age of patients at the moment of operation was 45.0 (SD \pm 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.

Primary Outcome

The NDI decreased comparably in all treatment arms from 39.58 to 41.85 preoperatively to 14.62 \pm 3.1 (ACD), 22.5 \pm 3.6 (ACDF), and 22.7 \pm 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).

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

TABLE 1. Patient Demographics

	ACD	ACDF	ACDA	Total
Number (n)	83	83	85	251
Age, yr	45.1 \pm 6.6	44.9 \pm 8.3	45.1 \pm 7.8	45.0 \pm 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 \pm 3.8	26.5 \pm 4.7	26.8 \pm 4.1	26.5 \pm 4.2
Disc height, mm	5.7 \pm 1.1	5.6 \pm 1.4	6.0 \pm 1.3	5.8 \pm 1.3
NDI	39.3 \pm 15.1	39.0 \pm 14.1	41.1 \pm 16.5	39.8 \pm 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 \pm SD.

ACD indicates anterior cervical discectomy; ACDA, anterior cervical discectomy and arthroplasty; ACDF, anterior cervical discectomy and fusion; NDI, Neck Disability Index.

TABLE 2. Summarizing Table for Primary and Secondary Outcomes

NDI	Baseline		1 Year FU		2 Years FU	
	Mean	Std. Error	Mean	Std. Error	Mean	Std. Error
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	Mean	Std. Error	Mean	Std. Error	Mean	Std. Error
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	Mean	Std. Error	Mean	Std. Error	Mean	Std. Error
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	Mean	Std. Error	Mean	Std. Error	Mean	Std. Error
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	Mean	Std. Error	Mean	Std. Error	Mean	Std. Error
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 1 year and after 2 years, with standard errors. Scores were computed using Generalized Estimated Equations to account for correlation between repeated measurements, missing values and study hospital.

ACD indicates anterior cervical discectomy; ACDA, anterior cervical discectomy and arthroplasty; ACDF, anterior cervical discectomy and fusion; MCS, mental component summary score; MPQ, McGill pain questionnaire; NDI, Neck Disability Index; NWC, total number of words chosen in the sensory, affective, and evaluative subscales; PCS, physical component summary score; PRI, pain rating index.

TABLE 3. Mean Differences for the Treatment Groups After 2 years for all Outcome Variables

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

ACD indicates anterior cervical discectomy; ACDA, anterior cervical discectomy and arthroplasty; ACDF, anterior cervical discectomy and fusion; MCS, mental component summary score; MPQ, McGill pain questionnaire; NWC, total number of words chosen in the sensory, affective, and evaluative subscales; PCS, physical component summary score; PRI, pain rating index.

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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 post-operatively (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.

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 2 Years

	Mean Difference	95% CI Lower Bound	95% CI Upper Bound	
ACDF versus 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 > 5.0mm	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 versus 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 > 5.0mm	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 versus 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 ≤ 5.0mm	3.382	-6.58	13.34	P = 0.506
Disc > 5.0mm	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 means between groups after 2 years. Scores were computed using Generalized Estimated Equations to account for correlation between repeated measurements, missing values, and study hospital. Values for the whole group, not divided into subgroups, are bold.

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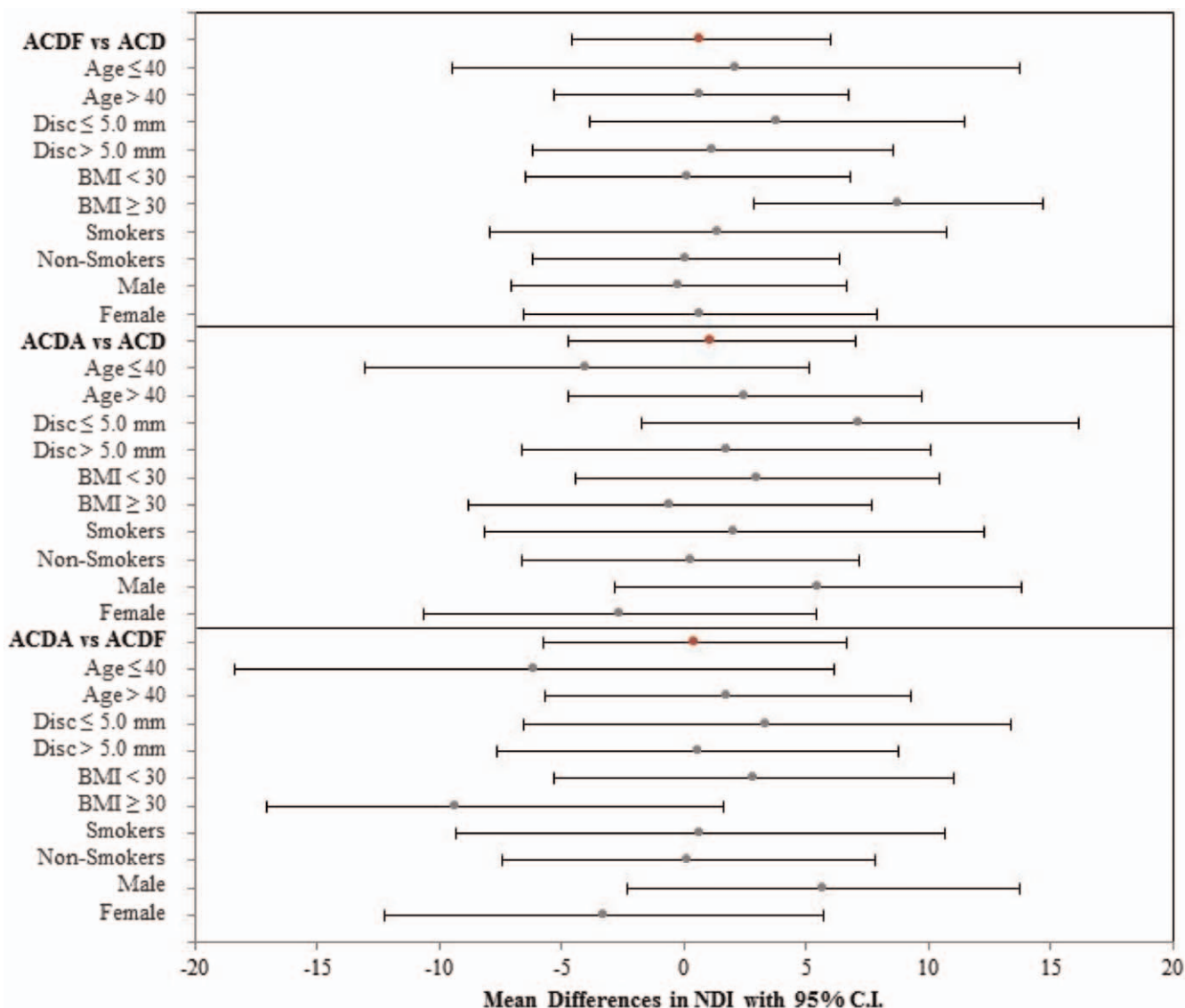


Figure 1. Mean differences in NDI for all subgroups per treatment group. Summarizing figure with mean differences in NDI after 2 years, based on the differences between marginal mean values with minimal and maximal mean differences (95%) for all treatment groups and subgroups. NDI indicates Neck Disability Index.

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 2 years follow up a clinical advantage for the cervical disc prosthesis is absent, when compared with the golden standard ACDF. Superior outcome after ACDA could not even be confirmed when ACDA was compared with ACD. Additionally, preliminary subgroup analysis could not indicate a certain type of patient that would benefit more from receiving the prosthesis 2 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

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TABLE 5. Complications and Reoperations

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)
Reoperations	ACD			ACDF			ACDA		
	NECK	Procon	Combined	NECK	Procon	Combined	NECK	Procon	Combined
Surgery for adjacent segment disease	2 [¶] (5.3)	3 (6.7)	5 (6.0)	3 (8.3)	5 (10.6)	8 (9.6)	2 [¶] (5.7)	0 (0)	2 (2.4)
Surgery for recurrent compression at index level*	1 [†] (2.6)	1 [‡] (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 [§]	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. Reoperations 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.

*Surgery for recurrent compression at index level was subdivided under “anterior” and “posterior.”

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

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

[§]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 recurrent stenosis at the index level.

[¶]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.

ACD indicates anterior cervical discectomy; ACDA, anterior cervical discectomy and arthroplasty; ACDF, anterior cervical discectomy and fusion.

intervals found in this study suggest that placement of an intervertebral device might not be 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 10-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 2 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 2 years and that this would have subsequent clinical outcome effects. Even though the Procon trial 9-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 one patient remained kyphotic; the other six patients recovered to a straight or lordotic spine during 2 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 2 years have to be interpreted cautiously, and 5-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,

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in terms of clinical outcomes after surgery. This supports our belief that both prostheses can be validly compared with each other.

Another limitation is the combined compliance rate of 63% after 2 years. With 159 patients having a complete follow-up record after 2 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 seven additional patients would have been needed at this follow-up moment to achieve the sample size number from the *post 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.³⁸ In determining the values for MCID we attempted to base the used values on different publications, each using different methods to approximate MCID.^{24,29-39}

Results from this study demonstrate that there is no clinical benefit for ACDA, when compared with ACDF or ACD 2 years after surgery. The small differences with narrow confidence intervals found in this study, especially for the ACDA *versus* ACD and ACDF *versus* 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 5-year and 10-year clinical and radiological results of this study should provide additional information about long-term effects of the three treatment strategies.

Key Points

- This study combined two randomized, double-blinded clinical trials on anterior decompression in cervical radiculopathy and demonstrated that a clinical ACDA is absent, when compared with the golden standard; ACDF or even ACD 2 years after surgery.
- The small differences with narrow confidence intervals found in this study after 2 years, especially for the ACDA *versus* ACD and ACDF *versus* ACD comparison, are surprising and suggest that ACD should not be ruled out in future comparative research.
- Additionally, preliminary subgroup analysis could not indicate a certain type of patient that would benefit more from ACDA.

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