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

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Chapter 2

Cervical radiculopathy: is a prosthesis preferred over fusion surgery?

A systematic review

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Abstract

Background

Meta-analyses on the comparison between fusion and prosthesis placing in the treatment of cervical radiculopathy mainly analyse studies including mixed patient populations: patients with radiculopathy with and without myelopathy. The outcome for patients with myelopathy is different compared to those without. Furthermore, apart from decompression of the spinal cord, restriction of motion is one of the cornerstones of the surgical treatment of spondylotic myelopathy. From this point of view the results for arthroplasty might be suboptimal for this category of patients. Comparing clinical outcome in patients exclusively suffering from radiculopathy is therefore a more valid method to compare the true clinical effect of the prosthesis to that of fusion surgery.

Aim

The objective of this study was to compare clinical outcome of cervical arthroplasty (ACDA) to the clinical outcome of fusion (ACDF) after anterior cervical discectomy in patients exclusively suffering from radiculopathy, and to evaluate possible differences with mixed patient populations.

Methods

In October 2018 a literature search was completed in Pubmed, Embase, Web of Science, COCHRANE, CENTRAL and CINAHL using a sensitive search strategy. Studies were selected by predefined selection criteria (a.o. patients exclusively suffering from cervical radiculopathy) and risk of bias was assessed using a validated Cochrane Checklist adjusted for this purpose. An additional overview of results was added from articles considering a mix of patients suffering from myelopathy with or without radiculopathy.

Results

Eight studies were included that exclusively compared intervertebral devices in radiculopathy patients. Additionally, 29 articles concerning patients with myelopathy with or without radiculopathy were studied in a separate results table. All articles showed intermediate to high risk of bias. In the radiculopathy patients a decrease in mean NDI score to 20.6 was reported in the prosthesis group, which was comparable to the mean NDI score of 20.3 in the fusion group, neither was there a clinically important difference in neck pain (VAS). Comparing these data to the mixed population data demonstrated comparable mean values, except for the two-year follow-up NDI values in the prosthesis group: mixed group patients that received a prosthesis reported a mean NDI score of 15.6, indicating better clinical outcome than the radiculopathy patients that received a prosthesis.

Conclusions

ACDF and ACDA are comparably effective in treating cervical radiculopathy due to a herniated disc in radiculopathy patients. Comparing the 8 radiculopathy with the 29 mixed population studies demonstrated that no clinically relevant differences were present in clinical outcome between the two types of patients.

Introduction

Anterior cervical discectomy with fusion (ACDF) is considered the standard surgical treatment for cervical radiculopathy. Decompressing the nerve root aims to diminish radicular complaints and adding a cage to the intervertebral space aims to maintain foraminal height and cervical alignment [1-3]. In the past three decades the use of a disc prosthesis (ACDA) is being investigated as an alternative treatment for patients with symptomatic cervical radiculopathy caused by cervical disc herniation. The rationale for the use of a prosthesis is to avoid loss of motion at the target level, which is a consequence of treating radiculopathy with ACDF. It is hypothesized that loss of motion causes neck disability and increased mechanical stress at the adjacent levels, possibly causing acceleration of degeneration at these adjacent segments (adjacent segment degeneration; ASD) [4, 5].

Comparing the results of ACDF and ACDA has been done before in systematic reviews and meta-analyses. An overview of Bartels et al. (2017) considered 21 meta-analyses in which the included studies tended to conclude that ACDA gave a better outcome, but differences were small and not clinically relevant [6]. However, it appeared that the meta-analyses considered mainly randomized controlled trials (RCTs) that were performed on mixed patient populations: patients suffering from radiculopathy with or without myelopathy. The outcome for patients with myelopathy is different compared to those without. Furthermore, apart from decompression of the spinal cord, restriction of motion is one of the cornerstones of the surgical treatment of spondylotic myelopathy. From this point of view the results for arthroplasty might be suboptimal for this category of patients. Comparing the outcome of fusion versus prosthesis in myelopathy patients may therefore have a different outcome than evaluation of outcome in patients exclusively suffering from radiculopathy.

In this review, only studies that discuss clinical findings exclusively in patients with complaints of radiculopathy, excluding myelopathy, are evaluated. Additionally, outcome of these findings will be compared to clinical outcome reported in the articles considered in the meta-analyses that evaluate mixed patient populations.

Materials and methods

Literature search strategy

The initial literature search strategy was performed in PubMed, EMBASE, Web of Science, COCHRANE, CENTRAL and CINAHL on August 2nd, 2016 and all English- and Chinese-language publications on the comparison of ACDF and ACDA were retrieved. Two of the authors separately evaluated the articles by title, abstract or full text, when necessary, to select the studies that met the predefined selection criteria. One author translated two relevant articles from Chinese to English. The search strategies used in the different databases were based on the search string as shown in Figure 1.

("Cervical Vertebrae"[mesh] OR "Cervic"[tw] OR "cervical"[tw] OR "neck"[mesh] OR "neck"[tw]) AND ("Intervertebral Disc Displacement"[mesh] OR "Slipped disk"[tw] OR "Slipped disks"[tw] OR "Slipped disc"[tw] OR "Slipped discs"[tw] OR "Prolapsed disk"[tw] OR "Prolapsed disks"[tw] OR "Prolapsed disc"[tw] OR "Prolapsed discs"[tw] OR "Herniated disk"[tw] OR "Herniated disks"[tw] OR "Herniated disc"[tw] OR "Herniated discs"[tw] OR "hernia"[tw] OR "Disc Displacement"[tw] OR "Disc Displacements"[tw] OR "Disk Displacement"[tw] OR "Disk Displacements"[tw]] OR "displaced disk"[tw] OR "displaced disks"[tw] OR "displaced disc"[tw] OR "displaced discs"[tw] OR "Radiculopathy"[Mesh] OR "Radiculopathies"[tw] OR "Radiculopathy, Cervical"[tw] OR "Cervical Radiculopathies"[tw] OR "Cervical Radiculopathy"[tw] OR "Radiculopathies, Cervical"[tw] OR "Radicular pain"[tw])

AND

("Diskectomy"[mesh] OR "Diskectomy"[tw] OR "Diskectomies"[tw] OR "Discectomy"[tw] OR "Discectomies"[tw] OR "Surgical Procedures, Operative"[mesh] OR "Surgical"[tw] OR "Operative"[tw] OR "Operation"[tw] OR "Operations"[tw] OR "Foraminotomy"[mesh] OR "Foraminotomy"[tw] OR "surgery"[subheading] OR "surgery"[tw] OR "surgic"[tw])

AND

("Diskectomy"[mesh] OR "Diskectomy"[tw] OR "Diskectomies"[tw] OR "Discectomy"[tw] OR "Discectomies"[tw] OR "Surgical Procedures, Operative"[mesh] OR "Surgical"[tw] OR "Operative"[tw] OR "Operation"[tw] OR "Operations"[tw] OR "Foraminotomy"[mesh] OR "Foraminotomy"[tw] OR "surgery"[subheading] OR "surgery"[tw] OR "surgic"[tw]) AND ('prosthesis' OR "artificial disc" OR 'artificial disk')

AND

(randomized controlled trial OR controlled clinical trial OR randomized controlled trials OR random allocation OR double-blind method OR single-blind method OR clinical trial OR clinical trials OR "clinical trial" OR ((singl* OR doubl* OR trebl* OR tripl*) AND (mask* OR blind*)) OR "latin square" OR placebos OR placebo* OR random* OR "Research Design"[MeSH:noexp] OR comparative study OR evaluation studies OR follow-up studies OR prospective studies OR cross-over studies OR control* OR controlled* OR prospective* OR volunteer* OR randomised controlled trial OR randomised controlled trials OR randomized active control trials OR randomized active control trial OR randomised active control trials OR randomised active control trial OR "RaCT" OR "RaCTs" OR RCT OR RCTs OR control*[tw] OR "latin square" [tw] OR cross-over studies [mh] OR control[tw] OR "Evaluation Studies "[Publication Type] OR "Evaluation Studies as Topic"[Mesh] OR "Pragmatic Clinical Trial" OR "Pragmatic Clinical Trials")

Figure 1. Search strategy

Search strategy that was used to perform the literature search August 2, 2016.

Article selection was based upon the following criteria:

- The study compares ACDF to ACDA in one-level anterior discectomy.
- The study includes at least twenty patients in each treatment arm.
- The study provides follow-up data for at least two years.
- The study measures primary or secondary outcome in either the Neck Disability Index (NDI) or Visual Analogue Scale neck pain (VAS neck pain).
- The study only includes patients suffering from radiculopathy, excluding patients suffering from myelopathy.
- The article is not a meeting abstract.

Any discrepancy in selection between the reviewers was resolved in open discussion, and, if needed, a third reviewer was asked make a final decision. Reference screening and citation tracking were performed on the identified articles.

When the literature search was repeated in August 2017 a meta-analysis by Bartels et al. was found [6]. In this study 21 meta-analyses were evaluated that focused on the outcomes of one-level arthroplasty. The included meta-analyses primarily described studies that allowed inclusion of patients suffering from cervical myelopathy. In order to be complete in our overview, the studies described in the meta-analyses were evaluated additionally in separate mixed group tables. This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA Statement [7].

Quality assessment

The methodological quality of all studies (including those from the RCTs describing mixed populations) was assessed by three independent reviewers (XY, TJ, CG), using an adjusted version of the checklist for cohort studies of the Dutch Cochrane Center [8]. If there was no consensus about the assessment, a fourth reviewer (CVL) was consulted. The items reviewed in the assessment were: definition of patient group, for which a maximum of three points could be given, absence of information bias which could maximally be awarded with three points, absence of selection bias for which maximally one point could be given and absence of attribution bias or confounding which could maximally be awarded with two points. Studies could be maximally awarded 9 points. Studies were then divided into low (7-9 points), intermediate (5-6 points) or high (4 or less points) risk of bias.

Outcome measures

For matters of comparison the most frequently used outcome parameters were extracted in this systematic review; the Neck Disability Index (NDI) and the Visual Analogue Scale (VAS) for neck pain. In addition, data on reoperations and complications was collected.

The NDI is a ten-item scaled questionnaire on three different aspects of neck complaints: pain intensity, daily work related and non-work related activities. Each item is scored from 0 to 5, and the raw total score ranges from 0 (best score) to 50 (worst score) [9]. Several studies indicate a MCID for NDI of 20 points on a 100-point scale [10, 11]. As many authors choose to present NDI scores on a 100-point scale, the outcome scores in this article were converted to that scale.

The Visual Analogue Scale (VAS) is the most commonly used tool to assess pain intensity. 0 mm indicates 'no pain' and 100 mm indicates the 'worst pain imaginable'. According to literature, the minimal clinical important difference (MCID) is approximately 20 mm, or 2.0 on a 10 point scale [12]. As most articles presented the VAS scores ranging from 0 to 10, we chose to convert all VAS scores to that scale in order to properly analyze and compare the data. If articles reported the NRS scores for neck pain instead of the VAS, articles were nevertheless considered eligible for inclusion because the two scales are very similar. For reasons of comparability, a 'standard mean'

was calculated from all reported NDI and VAS values, this value should not to be confused with a 'weighted mean' as would be reported after pooling the data in a meta-analysis.

Level of evidence

The quality of evidence for all outcome parameters was evaluated using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach according to Atkins [13] and adapted from Furlan [14].

Results

Search results and study selection of studies describing radiculopathy patients

603 articles were identified, of which 357 original articles remained after removing duplicates. Titles and abstracts were screened, resulting in 42 eligible articles. These articles were read full-text and 14 studies met all inclusion criteria. Six articles were additionally excluded after meticulously investigating literature. The article from Burkus et al. [15] had to be excluded because it also contained patients suffering from myelopathy. The article reports on the seven-year results of a study comparing ACDF versus prosthesis. The study population seemed to consist of patients with only radiculopathy. However, while searching for earlier follow up results from this study, the article describing the two-year follow-up results of this population was found [16]. From that particular article it was clear that the study population was a mixed one, also including patients with myelopathy and therefore Burkus' article was excluded.

Five of the remaining 12 studies, concerned the same RCT comparing Prodisc-C versus ACDF (autograft bone and plate). Therefore, the four studies with shorter follow up time were excluded (one with two-year, one with four-year, one with five- and one with seven-year follow up results) [17-20]. We decided to only include the article describing the seven-year results (the longest follow-up period) without the continued access group [21]. Additionally, one more study was excluded since it described the one-year follow up results [22], while the three-year follow-up results [23] were also available; 8 studies remained that fulfilled all inclusion criteria (Figure 2, Figure 3).

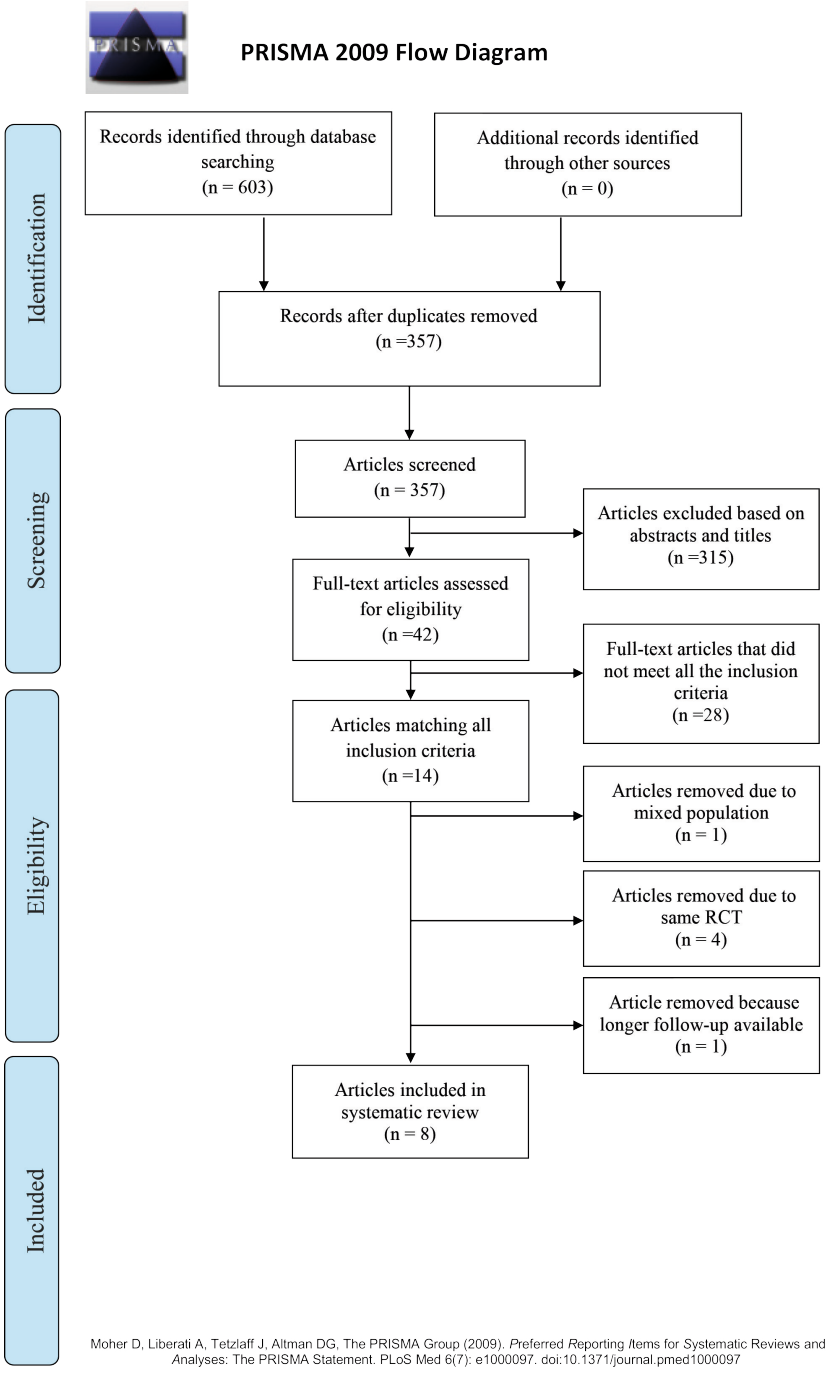

Figure 2. Flow chart of article selection process radiculopathy articles

Flow chart describing the search process for the articles exclusively including patients suffering from cervical radiculopathy.

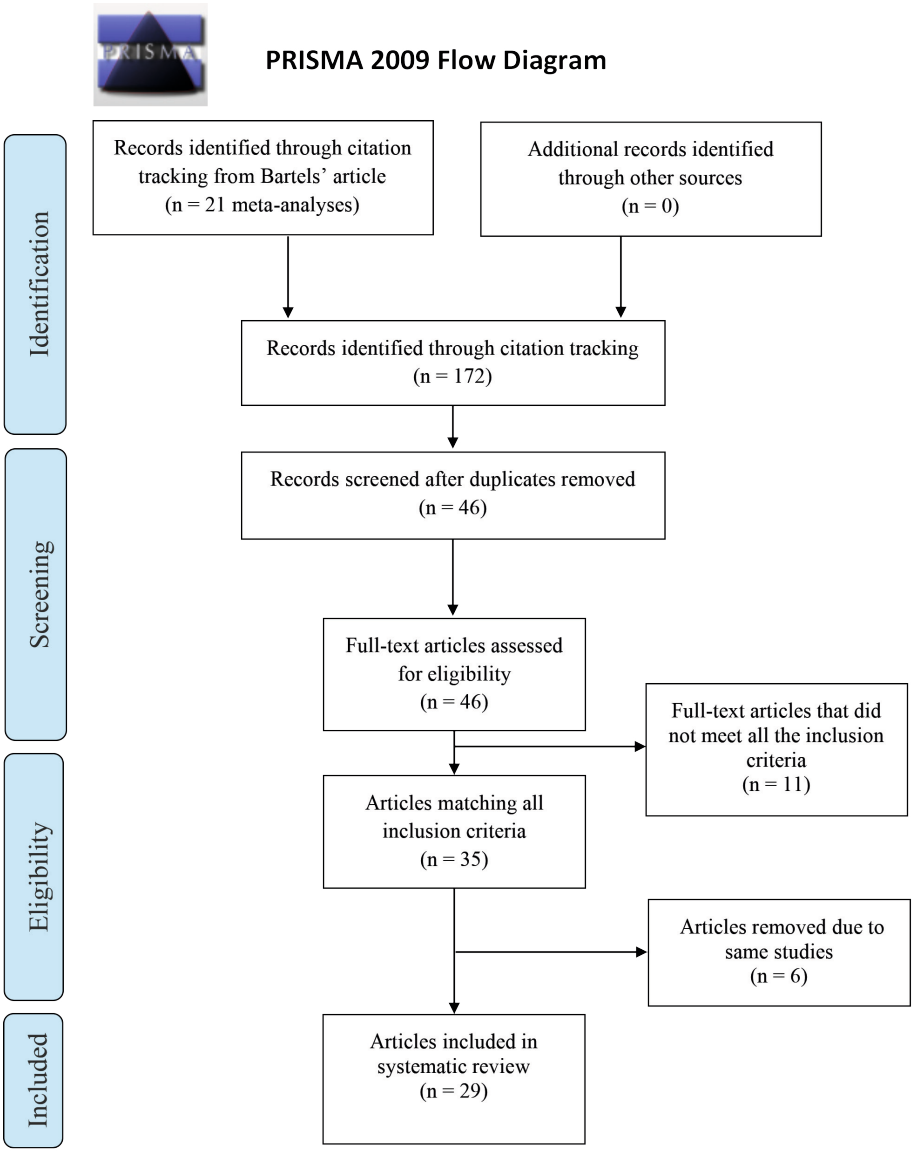

Figure 3. Flow chart of article selection process radiculopathy articles

Flow chart describing the search process for the articles including patients suffering from cervical myelopathy without radiculopathy.

Two RCTs described results on the Mobi-C prosthesis in comparison to ACDF methods using autograft alone [24] and securing with a plate [25]. Additionally, there was 1 retrospective study (Mobi-C vs PEEK cage without plate) [26] and 1 prospective cohort study comparing different types of prostheses (Prestige ST, Bryan, Prodisc-C) [27] versus ACDF (PEEK cage without plate). Two other RCTs compared the Prodisc-C prosthesis to ACDF with plate fixation [21, 23] and one RCT compared the Bryan prosthesis or Kineflex|C to ACDF with plate [28]. Lastly, one article described the comparison between the Discover prosthesis and a PEEK cage without plate [29]. The mean number of patients per group in the 8 included trials was 48. The mean age of the patients was 44.7 (ACDA) and 45.4 (ACDF) years old and the percentage of male patients was 46.1% (ACDA) and 49.0% (ACDF) (Table 1).

Year of publication, study type, prosthesis type, number of patients in each group, mean age for each treatment group, percentage of males and the follow-up period represented for the studies exclusively including patients suffering from cervical radiculopathy.

Search results and study selection of studies describing mixed patient groups

From the 21 meta-analyses retrieved form Bartels' article, 172 articles were found eligible for screening and after duplicates were removed 46 remained for full-text assessment. One article was selected for analysis in the radiculopathy group, as it described a population of patients from which myelopathy patients were excluded. Ten other articles were excluded because they did not report on the relevant clinical outcome measures or solely on radiological outcome parameters. Lastly, from the 35 articles that matched all inclusion criteria six articles had to be removed because they reported on the same RCTs, in which case we chose to include the article describing the longest follow-up period. Finally, 29 articles were found eligible for the mixed group overview, all reporting on the comparison between ACDA and ACDF in patients suffering from myelopathy with or without radiculopathy [15, 30-57]. In the 29 included articles the mean follow-up period was three years, mean number of patients per group was 90 (ACDA) and 78 (ACDF) and the mean age 45 (ACDA) and 46 (ACDF) years old. Study characteristics for each individual study can be found in Table 2.

Table 1. Study demographics radiculopathy studies

Study (year of publication)	Study design	Prosthetic device	Number of participants		Age (mean ± SD)		Men (%)		Follow-up (years)
			ACDA	ACDF	ACDA	ACDF	ACDA	ACDF	
Coric (2013)	RCT	Bryan, Kineflex|C	41	32	49.5	49.3	39	44	5
Hou (2016)	RCT	Mobi-C	51	48	46.3 ± 7.8	48.5 ± 8.3	58.8	58.3	5
Janssen (2015)	RCT	ProDisc-C	103	106	42.1 ± 8.42	43.5 ± 7.15	45	46	7
Nabhan (2007)]	RCT	ProDisc-C	21 †	20 †	44 [a]	44 [a]	56.1 [a]	56.1 [a]	3
Park (2008)	Retrospective	Mobi-C	21	32	45	47	52.4	62.5	1
Sala (2015)	Prospective cohort study	Prestige ST, Bryan or Prodisc-C	28	27	41	41	25	33.3	2
Sundseth (2017)	RCT	Discover	68	68	44.7	43.4	47.1	45.6	2
Zhang (2014)	RCT	Mobi-C	55	56	44.8	46.7	45.5	46.4	4
Mean			**48**	**48**	**44.7**	**45.4**	**46.1**	**49.0**	**3.6**

SD: standard deviation, ACDA: Anterior cervical discectomy with arthroplasty, ACDF: Anterior cervical discectomy and fusion, NA: Not available
[a]: Mean value for all participants † 41 patients in total, division between groups not clear.

Table 2. Study demographics mixed population studies

Study (year of publication)	Intervention	Follow-up (years)	Number of participants		Age (mean ± SD)	
			ACDA	ACDF	ACDA	ACDF
Burkus (2014)	Prestige ST	7	276	265	43.3	43.9
Cheng (2011)	Bryan	3	41	42	47.2 ± 5.7	47.7 ± 5.8
Coric (2006)	Bryan	1	17	16	43	43
Coric (2010)	Bryan, Kineflex|C, Discover	2	57	41	46.6	46.3
Coric (2011)	Kineflex|C	2	136	133	43.7 ± 7.76	43.9 ± 7.39
Davis (2015)	Mobi-C	4	225	105	45.3 ± 8.1	46.2 ± 8.0
Ding (2012)	Prestige LP	2	40	38	40	38
Fay (2014)	Bryan	2	37	40	52.1 ± **9.1** *	63.0 ± **10.6** *
Garrido (2010)	Bryan	4	21	26	40	43.3
Gornet (2016)	Prestige LP	7	280	265	44.5±8.8	43.9±8.8
Grasso (2015)	Prodisc-C, Mobi-C	2	20	20	40.5	47.3
Hisey (2016)	Mobi-C	5	164	81	NA	NA
Hou (2014)	Discover	2	117	108	45.6	44.1
Hacker (2005)	Bryan	1	22	24	NA	NA
Jawahar (2014)	Kineflex-C, Mobi-C, Advent Cervical Disc	4	59	34	NA	NA
Kim (2009)	Bryan	1	39	26	43.6	47.4
Li (2014)	DCI	2	39	42	45.3 ± 8.6	49.5 ± 9.3
Phillips (2015)	PCM	5	218	185	45.3 ± 9.0	43.7 ± 8.3
Porchet (2004)	Prestige II	2	27	28	44 ± 8.9	43 ± 6.9
Riew (2008)	Prestige ST	2	59	52	53.5 ± 13.9	53.5 ± 16.9
	Bryan		47	41	52.0 ± 14.6	50.8 ± 18.8

Table 2. Study demographics mixed population studies (continued)

Study (year of publication)	Intervention	Follow-up (years)	Number of participants		Age (mean ± SD)	
			ACDA	ACDF	ACDA	ACDF
Riina (2008)	Prestige ST	2	10	9	40.8 ± 8.8	38.1 ± 4.9
Rozankovic (2017)	Discover	2	51	50	41.32 ± 8.80	41.94 ± 9.36
Sasso (2007)	Bryan	2	56	59	42.5 ± 7.8	46.1 ± 7.8
Sasso (2011)	Bryan	4	242	221	44.4	44.7
Steinmetz (2008)	Bryan, Prestige ST	2	47	46	44.3 ± 6.5	43.9 ± 8.3
Vaccaro (2013)	SECURE-C	2	151	140	43.4 ± 7.50	44.4 ± 7.86
Wang (2008)	Bryan	2	28	31	42	43
Yan (2017)	Bryan	8	29	39	48.83 ± 6.70	48.72 ± 7.33
Zhang (2012)	Bryan	2	60	60	44.77 ± 5.60	45.57 ± 5.83
Mean		**3**	**90**	**78**	**45**	**46**

Year of publication, prosthesis type, the follow-up period, number of patients in each group and the mean age for each treatment group represented for the studies including patients suffering from both cervical radiculopathy and/or myelopathy.
* Reported statistical significant difference

Quality assessment

Quality assessment in radiculopathy studies

Only one article scored 7 out of 9 points, illustrating a low risk of bias [29], four articles scored five points [21, 24, 27, 28] and one scored 4 points [23] all indicating an intermediate risk of bias. The two remaining articles scored three points illustrating a high risk of bias [25, 26] (Table 3).

Table 3. Risk of bias for the radiculopathy studies

Author	Total risk of bias score	Well-defined patient group and study goal	Outcome properly examined	Absence of selection bias	Absence of attribution bias
Coric, (2013)	5*	**	*		**
Hou, (2016)	5*	**	*	*	*
Janssen, (2015)	5*	**	*	*	*
Nabhan, (2007)	4*	**		*	*
Park, (2005)	3*	**	*		
Sala, (2015)	5*	**	*	*	*
Sundseth, (2017)	7*	***	**	*	*
Zhang, (2014)	3*	**	*		
Mean score	4.63*				

Quality assessment in mixed studies

From the 29 studies there were two with a low risk of bias [36, 41], twenty-one with an intermediate risk of bias [15, 30, 31, 33-35, 38-40, 42-50, 54, 55, 57] and six with a high risk of bias [32, 37, 51-53, 56] (Table 4).

Table 4. Risk of bias for mixed group studies

Author	Total risk of bias score	Patient group and study goal	Outcome properly examined	Absence of selection bias	Absence of attribution bias
Burkus, (2014)	4*	***	*	-	-
Cheng, (2011)	5*	**	**	*	-
Coric (2006)	4*	**	*	-	*
Coric, (2010)	3*	**	*	-	-
Coric, (2011)	4*	***	*	-	-
Davis, (2015)	5*	***	*	-	*
Ding, (2012)	4*	**	*	-	*
Fay, (2014)	7*	***	**	*	*
Garrido, (2010)	2*	**	-	-	-
Gornet (2016)	4*	***	*	-	-

Table 4. Risk of bias for mixed group studies (continued)

Author	Total risk of bias score	Patient group and study goal	Outcome properly examined	Absence of selection bias	Absence of attribution bias
Grasso (2015)	5*	***	*	-	*
Hisey (2016)	4*	**	*	-	*
Hou, (2014)	7*	***	**	-	**
Hacker, (2005)	4*	**	*	-	*
Jawahar (2014)	6*	**	**	*	*
Kim, (2009)	5*	**	**	-	*
Li, (2014)	6*	**	**	-	**
Phillips, (2015)	4*	***	*	-	-
Porchet, (2004)	6*	***	*	*	*
Riew, (2008)	6*	***	**	-	*
Riina, (2008)	4*	**	*	-	*
Rozankovic, (2017)	4*	**	*	*	-
Sasso, (2007)	3*	**	*	-	-
Sasso, (2011)	2*	**	-	-	-
Steinmetz, (2008)	2*	**	-	-	-
Vaccaro, (2013)	4*	***	-	-	*
Wang, (2008)	4*	**	*	-	*
Yan, (2017)	3*	**	*	-	-
Zhang, (2012)	5*	***	**	-	-
Mean score	**4.34***				

The risk-of-bias-analysis represented in number of stars ('*'), the higher the number of stars the lower the risk of bias for each mixed group study.

Clinical outcome

Neck Disability Index (NDI)

Disability in articles describing exclusively radiculopathy patients

Six articles use the NDI as a scale to report on functionality [21, 24-26, 28, 29] (Table 5). All articles show a significant improvement in post-operative functionality compared to baseline, for both treatment groups. However, only one article shows a significant difference in NDI between the two treatment groups after two years. Though the reported statistically significant difference in that article is not clinically relevant, it shows a more favorable outcome for fusion, as compared to the prosthesis. The difference in mean NDI score after two years between the ACDA and ACDF group is 0.3 and the maximal reported difference is 3.8 [29].

Table 5. NDI and VAS outcome tables for radiculopathy studies

Study	Year	Mean NDI				VAS neck pain			
		Baseline		After 2 years follow-up		Baseline		After 2 years follow-up	
		ACDA	ACDF	ACDA	ACDF	ACDA	ACDF	ACDA	ACDF
Coric	2013	62.4	61.3	18.7	23.9	8 [d]	8 [d]	1.5 [d]	1 [d]
Hou [a]	2016	37 [a]	37.5 [a]	19 [a c]	18 [a c]	7.1 [a]	7.6 [a]	0.4 [a c]	0.5 [a c]
Janssen	2015	53.9 ± 15.1	52.3 ± 14.5	21.88	22.53	7.3 ± 1.95 [b *]	6.6 ± 2.17 [b *]	2.8 [b]	2.3 [b]
Nabhan	2007	NA	NA	NA	NA	6.0 ± 1.2	6.2 ± 0.9	1.8 ± 0.5	2.7 ± 0.4
Park	2008	45.8 [e]	46.9 [e]	20.1 [e]	16.7 [e]	4.85	6.11	1.9	2
Sala	2015	NA	NA	NA	NA	10	10	2	3
Sundseth	2017	45.7	51.2	25.0	21.2	7.0 [f]	7.0 [f]	3.0 [f]	3.0 [f]
Zhang [a]	2014	37.4	37.8	19.0	19.3	6.7	6.6	1.8 [a]	1.7 [a]
Mean		**47.0**	**47.8**	**20.6**	**20.3**	**7.1**	**7.3**	**1.9**	**2.0**

NDI (100 point scale) and VAS (10 point) scores at baseline and after two years for each study exclusively including patients suffering from cervical radiculopathy.
(*) reported stat sign difference [a] the value is estimated from the figure in articles NA: information not available [b] VAS score was based on the 100 or 20 point VAS-scale and modified (divided by 10 or 2) to fit this comparison [c] Three years follow-up results, as the two years follow-up was not available [d] Authors reported the median VAS-scores [e] NDI score was based on the 50 point NDI-scale and modified (multiplied by 2) to fit this comparison [f] Article reported NRS values for neck pain instead of VAS.

Level of evidence

The level of evidence is lowered by two levels, since most studies have an intermediate to high risk of bias. Furthermore, the findings are inconsistent as only one article presented a significant difference between the two groups, while the 5 other articles did not. Additionally, only one article succeeded in precisely stating the standard deviation (SD), but only for the baseline NDI estimate [21]. Three other articles provided information from which the SD could be calculated [24, 25, 29] while the remaining four did not [23, 26-28]. Therefore, the level of evidence that there is no difference in NDI improvement after 2 years follow up in radiculopathy patients is low.

Disability in articles describing mixed patient populations

26 articles use the NDI as an outcome parameter at baseline and after two years, three articles do not [31, 35, 42]. Five articles report a statistical significant difference between ACDF and ACDA two years after surgery in favor of the prosthesis, the difference is however never exceeding the MCID of 20. The difference between the mean NDI scores for ACDA and ACDF patients after two year is 4,2; but the maximal reported difference is 13,4 points on a 100-point NDI scale [48], a larger difference that is, however, still not clinically relevant (Table 6). In contrast to the vast majority of articles, three studies show a small difference in favor of fusion, though not statistically significant [44, 55, 56].

Level of evidence

The level of evidence is lowered by 3 levels. Findings are inconsistent, risk of bias is intermediate to high and data are not reported sufficiently precise. Additionally, the vast majority of studies received industry sponsoring and authors reported extensive disclosures, which enlarges the probability of reporting bias. Therefore, the level of evidence that there is no difference in NDI improvement after 2 years follow up in mixed population patients is very low.

Visual Analogue Scale (VAS) neck pain

VAS neck pain in articles describing exclusively radiculopathy patients

Seven of the eight articles used the VAS scale to grade neck pain and one article used the NRS score [29]. All articles showed that post-operative pain improved compared to baseline (Table 5). None of the articles demonstrated a statistically significant difference between the ACDA and ACDF group after two years.

Table 6. NDI and VAS outcome tables for mixed group studies

Study	Year	Mean NDI				VAS neck pain			
		Baseline		After two years of follow-up		Baseline		After two years of follow-up	
		ACDA	ACDF	ACDA	ACDF	ACDA	ACDF	ACDA	ACDF
Burkus	*2014*	55.7 ± 14.8	56.4 ± 15.9	20.0 ± 21.4	22.4 ± 21.5	NA	NA	NA	NA
Cheng	*2011*	50.6 ± 6.0	50.1 ± 5.8	13*[a]	17*[a]	NA	NA	NA	NA
Coric	*2006*	42[a]	47[a]	NA	NA	6.8[a b]	6.9[a b]	NA	NA
Coric	*2010*	61	62	19	25	7.12[b]	7.93[b]	2.67[b]	3.16[b]
Coric	*2011*	63.2	61.8	22.6	23.4	7.71[b]	7.57[b]	2.36[b]	2.42[b]
Davis	*2015*	54	56	17*	24*	7.1[a b]	7.4[a b]	1.6[a b]	2.0[a b]
Ding	*2012*	NA	NA	NA	NA	3.9 ± 2.5	4.4 ± 2.7	1.6 ± 1.0	1.8 ± 1.0
Fay	*2014*	36	43	15	22	4.8[a]	4.9[a]	1.8[a]	2.0[a]
Garrido	*2010*	51.1	51.5	12.4	19	7.62[b]	8.06[b]	1.79[b]	3.38[b]
Gornet	*2016*	55.5 ± 14.7	56.4 ± 15.9	16[a]	24[a]	6.07 ± 2.08[b]	6.93 ± 2.15[b]	1.0[a b]	1.9[a b]
Grasso	*2015*	21 ± 2.1	20.2 ± 6.4	5.4 ± 2.1	5.2 ± 3.2	7.02 ± 0.64[b]	7.1 ± 0.59[b]	1.03 ± 0.27[b]	1.07 ± 0.21[b]
Hisey	*2016*	55[a]	55[a]	17[a]	18.5[a]	7.1[a b]	7.0[a b]	1.8[a b]	2.0[a b]
Hou	*2014*	49.8 ± 19.7	51.2 ± 17.3	17.2 ± 13.4	18.3 ± 11.4	8.1 ± 1.1	8.2 ± 1.4	2.6 ± 1.0	3.1 ± 0.8
Hacker	*2005*	NA	NA	NA	NA	6.9[a b]	6.6[a b]	NA	NA
Jawahar	*2014*	61	60	14	25	8.0[b]	7.6[b]	1.9[b]	2.0[b]
Kim	*2009*	25.3 ± 1.8	25.5 ± 1.5	7.6 ± 0.9	7.2 ± 1.6	8.3 ± 1.0	8.3 ± 0.9	3.7 ± 0.9	3.8 ± 1.1
Li	*2014*	19.8 ± 7.2	21.8 ± 6.9	5.8 ± 2.9	10.2 ± 3.4	5.74 ± 1.58[b]	5.97 ± 1.67[b]	1.16 ± 1.09[b]	1.32 ± 1.17[b]
Phillips	*2015*	56[a]	55[a]	22[a]*	26[a]*	6.8	7.3	2.6[a b]*	3.0[a b]*
Porchet	*2004*	54[a]	60[a]	11[a]	23[a]	6.8[a b]	7.2[a b]	2.2[a b]	2.9[a b]

Table 6. NDI and VAS outcome tables for mixed group studies (continued)

Study	Year	Mean NDI				VAS neck pain			
		Baseline		After two years of follow-up		Baseline		After two years of follow-up	
		ACDA	ACDF	ACDA	ACDF	ACDA	ACDF	ACDA	ACDF
Riew *- Prestige ST* *- Bryan*	*2008*	53.5 ± 13.9 52.0 ± 14.6	53.5 ± 16.9 50.8 ± 18.8	21.4 ± 20.1 16.5 ± 16.7 *	22.4 ± 22.2 29.9 ± 26.3 *	6.8 [a b] 7.3 [a b]	6.8 [a b] 7.5 [a b]	1.7 [a b] 2.0 [a b]	1.5 [a b] 4.3 [a b]
Riina	*2008*	65.6 ± 11.7	60.2 ± 11.7	18.9 ± 16.8	22.3 ± 13.5	7.48 ± 1.94 [b]	7.16 ± 2.60 [b]	1.79 ± 2.41 [b]	1.74 ± 2.21 [b]
Rozankovic	*2017*	50.90 ± 11.48	51.20 ± 8.60	11.60 ± 4.44 *	19.68 ± 5.98 *	7.56 ± 1.36	7.5 ± 1.39	2.36 ± 0.75 *	3.46 ± 0.68 *
Sasso	*2007*	47	49	10	11	7.2 [b]	7.3 [b]	1.6 [b] *	3.2 [b] *
Sasso	*2011*	51.4 ± 15.3	50.2 ± 15.9	16.2 ± 18.5	19.2 ± 19.3	7.54 ± 1.99 [b]	7.48 ± 2.30 [b]	2.30 ± 2.77 [b]	3.03 ± 3.97 [b]
Steinmetz	*2008*	60.2	61.5	32 [a]	36 [a]	7.7 ± 1.6	8.0 ± 1.8	3.9 ± 3.2	3.9 ± 2.6
Vaccaro	*2013*	51.8 ± 13.84	51.5 ± 14.86	13 [a]	17 [a]	6.52 ± 2.68 [b]	6.34 ± 2.73 [b]	1.4 [a b]	2.0 [a b]
Wang	*2008*	43.5 ± 8.6	45.4 ± 7.6	8.9 ± 4.5	8.4 ± 5.1	6.3 ± 1.6	6.4 ± 1.2	2.2 ± 0.5	2.4 ± 0.6
Yan	*2017*	47.3 ± 7.1	48.6 ± 6.8	24.1 ± 3.8 [c]	23.8 ± 3.6 [c]	NA	NA	NA	NA
Zhang	*2012*	51.63 ± 7.18	54.53 ± 8.47	14.89 ± 2.90	15.25 ± 3.77	6.81 ± 0.81 [b]	6.88 ± 0.71 [b]	1.91 ± 0.50 [b] *	2.15 ± 0.49 [b] *
Mean		**49.5**	**50.3**	**15.6**	**19.8**	**6.9**	**7.1**	**2.0**	**2.5**

NDI (100 point scale) and VAS (10 point) scores at baseline and after two years for each study including both patients suffering from cervical radiculopathy or/and myelopathy.
(*) reported stat sign difference [a] the value is estimated from the figure in articles NA: information not available [b] VAS score was based on the 100 or 20 point VAS-scale and modified (divided by 10 or 2) to fit this comparison [c] Three years follow-up results, as the two years follow-up was not available [d] Authors reported the median VAS-scores [e] NDI score was based on the 50 point NDI-scale and modified (multiplied by 2) to fit this comparison [f] Article reported NRS values for neck pain instead of VAS.

Level of evidence

The level of evidence is lowered by 1 level, since most studies have an intermediate to high risk of bias. Moreover, only one study reports the exact standard deviations with every estimate [23]. Therefore, the level of evidence is moderate that there is no difference in neck pain improvement after implanting a cage or a prosthesis in cervical radiculopathy patients.

VAS neck pain in articles describing mixed patient populations

24 articles out of the 29 articles use the VAS neck pain as an outcome measure. All articles showed that neck pain improved post-operatively in comparison to baseline, in both treatment groups. Four articles report a statistically significant difference between the prosthesis and fusion in favor of the prosthesis [46, 50, 51, 57]. The maximal reported difference for VAS after two years was 2,3; while the difference between the mean values was 0.5. The discussed differences however never exceeded the MCID for VAS of 2,5 (Table 6).

Level of evidence

The level of evidence is lowered with 3 levels. All articles have an intermediate to high risk of bias, the vast majority of studies received industry sponsoring and authors reported extensive disclosures, which enlarges the probability of reporting bias. Furthermore, findings are inconsistent and, estimates of effect are not sufficiently precise as not all articles state the exact data. Therefore, the level of evidence that there is no difference in neck pain improvement after implanting a cage or a prosthesis in mixed population patients is very low.

Reoperations

Reoperation rate in articles describing exclusively radiculopathy patients

Seven of the eight articles reported reoperation rates, of which 2 articles report statistically significant differences in the rates. One study reports more reoperations in the fusion group [24] and the other higher rates in the prosthesis group [29]. Outcome reporting on the level of reoperation is rather heterogeneous and incomplete, however the results are suggesting that reoperations are most frequent at the adjacent level for the ACDF group and at the index level for the ACDA group (Table 7).

Reoperation rate in articles describing mixed patient populations

The majority of the articles report on "subsequent surgical interventions", which include revisions, removals and supplemental fixations. Two of the twenty-nine studies report statistically significant differences between the groups in terms of reoperation rates, both in favor of the arthroplasty group [40, 54].

Table 7. Number of re-operations and ASD incidence

Study	ACDA	ACDF	ACDA	ACDF
	Re-operations		ASD Incidence	
Coric (2013)	4/41	1/32	NA	NA
Index level	1	0		
Adjacent level	2	1		
Hou (2016)	1/51 *	7/48 *	1/51 *	7/48 *
Index level	0	NA	NA	NA
Adjacent level	1	NA	NA	NA
Janssen (2015)	13/103	31/106	1/103	2/106
Index level	6	8	NA	NA
Index and adjacent level	1	11	NA	NA
Adjacent level	6	22	NA	NA
Nabhan (2007)	0/17	1/24	0/17	1/24
Index level	0	0	0	0
Adjacent level	0	1	0	1
Park (2005)	NA	NA	NA	NA
Index level				
Adjacent level				
Sala (2015)	NA	NA	NA	NA
Index level				
Adjacent level				
Sundseth (2017)	8/68*	1/68*	NA	NA
Index level	8	1		
Adjacent level	0	0		
Zhang (2014)	1/55†	1/56×	1/55†	1/56×
Index level	0	0	0	0
Adjacent level	1	1	1	1

Number of re-operations and the level of re-operation in the left column and ASD incidence in number of patients/total number of patients in the treatment group.
*NA: information not available, * Reported statistically significant differences, † × Concerning the same patient*

Complications

Complications in articles describing exclusively radiculopathy patients

The most common complications, apart from reoperations, included; adjacent segment disease (ASD), trauma, ongoing neck and/or arm pain, dysphagia, hoarseness, musculoskeletal pain and infections. Complications were seldom permanent. Four articles described adjacent segment disease [21, 23-25], of which only one article described a significantly higher incidence of ASD in ACDF patients [24]. No other statistically significant differences in complication rates were described between the treatment groups.

Complications in articles describing mixed patient populations

Three articles report statistically significant differences in the incidence of complications; the first study found a higher incidence of device related complications in the ACDF group [48], the second study reported a higher rate of overall adverse events in the ACDA group [38] and the third article found more severe adjacent-level radiographic changes in the ACDF group [33]. Two other articles studied ASD very specifically but couldn't find statistically significant differences between the two treatment strategies [37, 56].

Heterogeneity

Pooling results from the eight radiculopathy articles was considered, however it was found that results were too heterogeneously reported for doing so. The number of studies was small, standard deviations were scarcely reported, p-values were mostly provided for the comparison between baseline and two years post-operatively within one treatment group instead of between the treatment group. Pooling the data would therefore require statistical imputation for the majority of the standard deviations and p-values. Articles were also clinically heterogeneous, as NDI and VAS scores were expressed on different scales and some articles reported the exact values after two years, while others reported the decline from baseline to two years or the difference between ACDA and ACDF at two years. Pooling results in mixed group articles has been done previously and is therefore likely not to lead to new insights [58-61]. Subsequently, this means that heterogeneity tests, such as the I2, were not performed, as data was not pooled.

Discussion

Meticulous literature research reveals that pain and disability scores were comparable in patients after two years and not dependent on receiving either a cage or a prosthesis, after anterior cervical discectomy for radiculopathy. Likewise, no difference in outcome scores was found between these surgical interventions in mixed patient populations. The same was true for the reoperation rates and the incidence of adjacent segment degeneration (ASD). After using the GRADE approach, the level of evidence for absence of a difference in neck pain and disability in radiculopathy patients is higher than the level of evidence in the mixed patient population, however the overall level of evidence was low. This conclusion is in line with a meta-analysis by Bartels from 2010, that demonstrates that most studies comparing ACDF and ACDA are not blinded and that a clinical benefit for the prosthesis is not proven [58].

Several other meta-analyses comparing ACDA and ACDF have been published [59-61]. These meta-analyses included mainly studies that did not exclude myelopathy patients. These patients are prone to have more severely degenerated cervical spines and perform different on outcome scales. It is therefore most striking that in this systematic review the mean NDI two years post-operatively is lower (better) in the ACDA group with both myelopathy and radiculopathy patients than in the ACDA group with radiculopathy patients. This phenomenon might suggest the presence of bias

due to industry sponsoring or lack of blinding. An alternative hypothesis could be that patients with more degenerated cervical spines are used to a certain amount of pain and therefore are more likely to report a better disability or pain score.

This review was set up as a counterweight to the 21 meta-analyses retrieved from Bartels' article on studies comparing ACDF and ACDA concluding that outcome in prosthesis implanted patients was slightly better than in patients that underwent cervical fusion, although not statistically significant nor clinically relevant. It was hypothesized that outcome could be more convincingly favorable for the prosthesis if only radiculopathy patients would be considered. However, the opposite conclusion had to be drawn. Not only were the results in radiculopathy patients not different in ACDA and ACDF patients, but careful analysis of literature on mixed patient populations demonstrated that results were comparable in that patient population too. The suggestion that is offered by most of the existing articles, that the prosthesis is clinically superior to fusion, is therefore most likely to be too optimistic.

Another argument that is often used in favor of the prosthesis is claim of superior radiological results in terms of ASD and Range Of Motion (ROM). However, a recent systematic review shows no convincing radiological evidence for superiority of the prosthesis in ASD [62]. Additionally, the authors stress the absence of solid evidence for a correlation between the increased incidence of ASD and worse clinical outcome.

A factor that might initiate bias is the outcome assessment as most studies, that report a statistically significant difference, use a combined success score to define which treatment arm performs better. These success scores always included an improvement in NDI or VAS score of a minimum number of points or a minimum percentage, but they also included reoperations and serious adverse events. Additionally, 'Neurological success' was often added into this success score, meaning that an evaluation conducted by the investigator for muscle strength, sensory assessments and reflex assessments was included. These investigator-conducted evaluations are prone to bias as the articles do not mention whether or not the investigator was blinded to the treatment the patient received. When these combined success scores are not taken into account, but only the plain clinical outcome measures and their statistical significance and clinical relevance, the inevitable conclusion is that ACDA is not superior to ACDF.

A strength of this systematic review is the strict distinction that is made between radiculopathy and myelopathy with or without radiculopathy (mixed) groups of patients. Previous studies evaluating literature on this topic did not separate radiculopathy and myelopathy patients and outcome was thus reported on heterogeneous groups. Furthermore, not only analyzing radiculopathy patient groups but adding the mixed group articles in a separate section allowed for a comparison between the two types of patients.

Based on clinical outcome measures, literature indicates that the results of ACDF and ACDA do not differ in the treatment of cervical radiculopathy. The results are not prominently different in patients suffering from myelopathy with or without radiculopathy. Further research should have more statistical power, should apply specific inclusion criteria to increase the external validity to specific

groups of patients, should blind both the patients and the outcome assessor and report long-term follow-up results in order to draw definitive conclusions on the clinical relevance of the prosthesis. With the increase of power the possibility of performing an additional subgroup analyses should be considered to identify possible subgroups that might benefit more from receiving a prosthesis.

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