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REVIEW ARTICLE

Long-term Results Comparing Cervical Disc Arthroplasty to Anterior Cervical Discectomy and Fusion: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Objective: Whether cervical disc arthroplasty (CDA) is superior to anterior cervical discectomy and fusion (ACDF) remains controversial, especially in relation to long-term results. The present study aimed to evaluate the long-term safety and efficiency of CDA and ACDF for cervical disc disease.

Methods: We performed this study according to the Cochrane methodology. An extensive search was undertaken in PubMed, Embase, and Cochrane databases up to 1 June 2019 using the following key words: "anterior cervical fusion," "arthroplasty," "replacement" and "artificial disc". RevMan 5.3 (Cochrane, London, UK) was used to analyze data. Safety and efficiency outcome measures included the success rate, functional outcome measures, adverse events (AE), adjacent segment degeneration (ASD), secondary surgery, and patients' satisfaction and recommendation rates. The OR and MD with 95% confidence interval (Cl) were used to evaluate discontinuous and continuous variables, respectively. The statistically significant level was set at P < 0.05.

Results: A total of 11 randomized controlled trials with 3505 patients (CDA/ACDF: 1913/1592) were included in this meta-analysis. Compared with ACDF, CDA achieved significantly higher overall success (2.10, 95% *Cl* [1.70, 2.59]), neck disability index (NDI) success (1.73, 95% *Cl* [1.37, 2.18]), neurological success (1.65, 95% *Cl* [1.24, 2.20]), patients' satisfaction (2.14, 95% *Cl* [1.50, 3.05]), and patients' recommendation rates (3.23, 95% *Cl* [1.79, 5.80]). Functional outcome measures such as visual analog score neck pain (-5.50, 95% *Cl* [-8.49, -2.52]) and arm pain (-3.78, 95% *Cl* [-7.04, -0.53]), the Short Form-36 physical component score (SF-36 PCS) (1.93, 95% *Cl* [0.53, 3.32]), and the Short Form-36 mental component score (SF-36 MCS) (2.62, 95% *Cl* [0.95, 4.29]), revealed superiority in the CDA group. CDA also achieved a significantly lower rate of symptomatic ASD (0.46, 95% *Cl* [0.29, 0.74]), and secondary surgery at the adjacent level (0.37, 95% *Cl* [0.28, 0.49]). However, no significant difference was found in radiological success (1.35, 95% *Cl* [0.88, 2.08]), NDI score (-2.88, 95% *Cl* [-5.93, 0.17]), total reported AE (1.14, 95% *Cl* [0.92, 1.42]), serious AE (0.89, 95% *Cl* [0.71, 1.11]), device/surgery-related AE (0.90, 95% *Cl* [0.68, 1.18]), radiological superior ASD (0.63, 95% *Cl* [0.28, 1.43]), inferior ASD (0.45, 95% *Cl* [0.19, 1.11]), and work status (1.33, 95% *Cl* [0.78, 2.25]). Furthermore, subgroup analysis showed different results between US and non-US groups.

Conclusion: Our study provided further evidence that compared to ACDF, CDA had a higher long-term clinical success rate and better functional outcome measurements, and resulted in less symptomatic ASD and fewer

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secondary surgeries. However, worldwide multicenter RCT with long-term follow up are still needed for further evaluation in the future.

Key words: Adjacent segment degeneration; Anterior cervical discectomy and fusion; Cervical disc arthroplasty; Cervical disc disease; Long-term

Introduction

nterior cervical discectomy and fusion (ACDF) has been Aviewed as the gold standard procedure for cervical disc disease (CDD), including radiculopathy and myelopathy. A recent survey revealed that 84.3% of surgeons performed ACDF as the standard technique for CDD¹. Even though successful clinical outcomes can be achieved with ACDF, postoperative complications such as pseudoarthrosis or nonunion, instrument failure, and adjacent segment degeneration (ASD) have been the greatest concerns²⁻⁴. Cervical fusion could lead to loss of range of motion at the index level and shift load to the adjacent level, then result in accelerating ASD^{2,3,5}. Hilibrand *et al.* reported that annually 2.9% of the patients underwent anterior interbody fusion will most likely develop ASD requiring cervical intervention². Thus, spinal surgeons have been attempting to find an alternative procedure to avoid these complications associated with ACDF.

A motion-preserving procedure, cervical disc arthroplasty (CDA), seems to be a good choice. CDA was initially designed using motion-preserving techniques to restore cervical physiologic biomechanical properties and alleviate the adjacent-level loads, and eventually reduces or eliminates the risk of developing ASD⁶. Clinical data showed that preoperative motion could be maintained in the long run following CDA⁷. Promisingly, recent studies have proved that CDA is cost-effective and is comparable to ACDF in long-term follow ups^{8–11}. However, some disadvantages of CDA cannot be overlooked, such as heterotopic ossification, implant failure, and bone loss^{12–14}. In addition, the revision burden of CDA was two times higher than that of ACDF¹⁵.

In the past 20 years, a series of randomized controlled trials (RCT) have been conducted; however, the reported results are inconsistent and have great variability. Although a few systematic reviews have been performed, researchers have failed to reach an agreement owing to varied criteria^{5,16–24}. Nevertheless, there is an absence of pooling of long-term results in a comprehensive meta-analysis. Therefore, this is the first study aiming at comparing CDA to ACDF with special focus on long-term safety and efficiency. The conclusions drawn from this study could provide solid evidence for the future application of CDA.

This study was approved by the Ethics Committee of The Second Xiangya Hospital of Centeral South University.

Methods

Literature Search Strategy

We followed the Cochrane methodology guidelines to perform this meta-analysis and searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CCRCT) databases up to 1 June 2019. The keywords "anterior cervical fusion," "arthroplasty," "replacement," and "artificial disc" combined with "and/or" were used to identify any relevant studies.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (i) patients \geq 18 years old with symptomatic CDD presenting with radiculopathy and/or myelopathy; (ii) participants were treated with either CDA or ACDF; (iii) comparison was performed between CDA and ACDF; (iv) at least one efficiency and safety outcome measurement was available; and (v) prospective RCT with a follow up \geq 5 years.

Articles that met the following characteristics were excluded: (i) reviews, case reports or series, editorials, conference abstracts, and retrospective studies; (ii) duplicated data publications from the same RCT; (iii) partial results with insufficient data; and (iv) non-English publications.

Literature Screening

Literature screening was performed by two independent investigators (Tu, ZM and Wang, QL). Any disagreement was discussed with another author (Hu, P) to reach consensus. After excluding duplicates, literature selection was carried out according to the inclusion and exclusion criteria based on title and abstract. Then, extensive screening of fulltext articles was performed. All RCT that compared the long-term efficiency and safety of CDA and ACDF for CDD were included.

Quality Assessment of the Included Studies

Quality assessment was achieved using the criteria recommended by the Cochrane Back Review Group criteria²⁵. The types of biases assessed are: four selection bias, four performance bias, two attrition bias, one detection bias, and one reporting bias. The articles scoring at least 6 of these 12 biases were considered as at low risk of bias. The last bia assessed is "Other," defined as any potential bias not detected using the previous criteria.

Data Extraction

Data extraction was performed as follows: (i) general characteristics such as first author, year of publication, number of clinical trial (NCT), enrolled patients, follow-up rate, age, sex, surgical levels, type of prosthesis, and follow-up duration were extracted; and (ii) outcome measures, including clinical success rate (overall success, NDI success, neurological success, and radiological success), functional outcome

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measurements (NDI score, visual analog score [VAS] neck pain and arm pain, and SF-36 PCS and MCS), AE (total reported AE, serious AE and device/surgery-related AE), ASD (symptomatic ASD, radiological superior or inferior ASD), secondary surgery (total secondary surgery, secondary surgery at the index level and at the adjacent level), work status, and patients' satisfaction and recommendation rates were extracted. This task was performed by two independent investigators (Tu, ZM and Wang, QL), who extracted the data and discussed any disagreement to reach consensus with a third investigator (Hu, P). Data-extracting software was used to obtain data from figures when original data was not available²⁶.

Statistical Analysis

RevMan 5.3 (Cochrane, London, UK) was used to pool extracted data into a combined analysis. The odds ratio (OR) and mean difference (MD) with 95% confidence intervals (CI) were used to evaluate discontinuous and continuous variables, respectively. Heterogeneity was assessed using a χ^2 -test and an I^2 -test. A fixed effects model was used when $I^2 < 50\%$; otherwise, a random effects model was used. Sensitivity analysis was performed by comparing two different effects models.

If the statistical difference changed, the leave-one-out method²⁷ and subgroup analysis was performed to find the origin of heterogeneity. Funnel plots were applied to assess for publication bias. A statistically significant difference was defined as a *P*-value of less than 0.05.

Results

Literature Review

Initial database searching identified 1954 articles (PubMed: 650, Embase: 1020, CCRCT: 284) and detailed literature screening is described in the flow diagram in Figure 1. A total of 814 studies were removed because they were duplicates, 1076 studies were excluded based on their titles and abstracts, and 43 studies were excluded for other reasons. As a result, 21 studies^{28–48} were included for further evaluation. Among them, 2 studies^{45,47} were partial results of multicenter RCT and 8 studies^{39–44,46,48} included duplicated data for publication. Ultimately, 11 articles^{28–38} involving 3505 patients (CDA/ACDF: 1913/1592) were included in this meta-analysis. There are 923 male and 990 female patients in the CDA group and 791 male and 801 female patients in the ACDF group. The mean age of each included population varies from 40 to



50 years in both groups. All the patients suffered from radiculopathy and/or myelopathy caused by cervical disc disease with C_{3-4} to C_{6-7} involvement. The basic characteristics of the included studies and patients are summarized in Table 1. Among them, 8 studies^{28–30,32–34,36,38} compared single-level CDD, 1 study³¹ compared two-level CDD, and 2 studies^{35,37} compared both single-level and two-level CDD independently.

Quality Assessment of the Included Studies

Methodological quality assessment of the 11 eligible studies is shown in Fig. 2. Nine studies^{28,30-37} were adequately randomized, but 1 study²⁹ did not provide detailed information of randomization, and 1 study³⁸ failed to achieve adequate randomization. Only 4 studies^{30,32,33,35} provided a clear statement regarding avoiding allocation concealment. In addition, all included RCT²⁸⁻³⁸ failed to achieve blinding to patients and care providers due to the specialty of this kind of trial. The patients were informed immediately after surgery about the type of surgical procedure they had been underwent, and care providers were aware of which kind of surgery was to be performed during surgery^{28,30-37}. Almost all the studies described the dropout rate and 2 studies^{28,29} with a followup rate below 70% were considered as having high risk of bias. All included studies were scored above seven and were rated as having low risk of bias.

Heterogeneity Analysis

Of all the parameters identified for meta-analysis, 6 studies compared overall success^{28,29,31,34,37,38} and NDI success^{28,31,34,36–38}, 7 studies compared neurological success^{28,31,33,34,36–38}, 3 studies compared radiological success^{31,36,37}, 7 studies compared NDI score^{28,32,33,35–38}, 5 studies compared neck pain score^{33,35–38}, 4 studies compared arm pain score ^{33,35–37}, 5 studies compared SF-36 PCS^{28,30,33,36,38}, 4 studies compared SF-36 MCS^{30,33,36,38}, 8 studies compared any AE^{28–31,33,36–38}, 4 studies compared serious AE^{31,36–38}, 6 studies compared device/surgery-related AE^{29,31,33,36–38} and symptomatic ASD^{30,33–35,37,38}, 2 studies compared radiological superior and inferior ASD^{37,38}, 8 studies compared total secondary surgeries^{28–30,32,33,35–37} and secondary surgeries at the index level^{28,30,31,33,35–38}, 9 studies compared secondary surgeries at the adjacent level^{28,30,31,33–38}, 2 studies compared work status^{28,34}, 4 studies compared patients' satisfaction rate^{31,36–38}, and 2 studies compared patients' recommendation rate^{36,37}.

The heterogeneity test showed that $I^2 < 50\%$ for overall success, NDI success, neurological success, radiological success, VAS neck pain and arm pain, SF-36 PCS and MCS, total reported AE, serious AE, device/surgery-related AE, symptomatic ASD, secondary surgery at the adjacent level, and patients' satisfaction and recommendation rates. This indicates that there is low heterogeneity among these parameters and a fix effects model could be applied for combined statistics. In contrast, the heterogeneity test showed $I^2 > 50\%$ for NDI score, radiological superior and inferior ASD, total secondary surgery, secondary surgery at the index level, and work status, which indicates significant or large

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	evel Pi		
	BMI (CDA/ACDF)	/ 27.5(5.0)/28.7(5.7) / 28.2(5.6)/28.6(4.9) 21(3.2)/22(2.5) 26.44(5.32)/27.34(5.54) 26.6(4.8)/27.4(4.8) 26.26 28.2(6,27.4(4.8) 27.3(4.6)/27.4(4.8) 28.3(4.5)/29.0(5.47) 28.9(5.53)/29.0(5.47)	ical disc arthroplasty.
	Sex (female)	148/142 74/74 26/22 117/98 30/28 55/54 132/108 42/33 105/89 78/36 113/45 70/72	dex; CDA, cerv
	Age (CDA/ACDF)	43.3/43.9 43.7(7.76)/43.9(7.39) 44.1(6.4)/43.1(7.5) 47.1(8.3)/47.3(7.7) 46.3(7.8)/48.5(8.3) 42.1(8.42)/43.5(7.15) 42.4(44.7) 42.4(44.7) 43.3(9.2)/44.0(8.2) 43.3(9.2)/44.0(8.2) 43.3(7.50)/44.4(7.86)	usion; BMI, body mass in
	Follow-up rate (CDA/ACDF)	76.8%/69.1% 68.4%/62.4% 98.0%/97.9% 91.1%/94.1% 92.%/92% 100%/100% 89.2%/87.1 75.8 80.1%/75.3% 86.1%/84.2%	liscectomy and fu
	Enrolled patients (CDA/ACDF)	276/265 136/133 50/47 50/47 209/188 56/51 103/106 242/221 242/221 242/185 164/81 225/105 151/140	erior cervical d
	Design	RCT, 31-sites RCT, 21-sites RCT, 21-sites RCT, 30-sites RCT, 30-sites RCT, 13-sites RCT, 13-sites RCT, 24-sites RCT, 24-sites RCT, 24-sites RCT, 18-sites RCT, 18-sites	study.; ACDF, ante
uded studies	Number of clinical trial	NCT00642876 NCT005374413 ISRCTN41681847 NCT00637156 Unknown NCT00291018 NCT00437190 ISRCTN44347115 Unknown NCT00389597 NCT00389597 NCT00389597 NCT00389597 NCT00389597) are from the same
ristics of inclu	Region	USA USA Netherlands USA U.S. Sweden USA USA USA USA USA	Radcliff (2017b
TABLE 1 Characte	Study	Burkus 201 4^{28} Coric 201 8^{29} Donk 201 7^{30} Gornet 201 9^{31} Hou 201 6^{32} Janssen 201 5^{33} Lavelle 201 8^{34} MacDowall 201 9^{35} Phillips 201 2^{36} Radcliff 201 $7a^{37*}_{1}$ Radcliff 201 $7a^{37*}_{1}$	*Radcliff (2017a) and

	Adequate randomization	Allocation concealment	Blinding of patients	Blinding of care provider	Blinding of outcome assessment	Acceptable drop-out rate	Intention-to-treat analysis	Free of selective reporting	Similar baseline data	Avoid or simar cointervention	Acceotable compliance	Timing of assessment	Other bias
Burkus (2014)	+	?		?	?	+		+	+	+	+	+	+
Coric (2018)	?	?	?	?	+			ŧ	ŧ	+	+	+	+
Donk (2017)	+	+	?		?	+	+	ŧ	ŧ	+	+	+	+
Gornet (2019)	+	?			+	+	+	+	+	+	+	+	+
Hou (2017)	+	+			+	+			ŧ	+	+	+	+
Janssen (2015)	+	+			?	+		+		+	+	+	+
Lavelle (2018)	+	?	•		?	•		+	•	+	+	+	+
MacDowall (2019)	+	+	•	•	+	+	+	+	+	+	+	+	+
Phillips (2015)	+	?			•	+	+	+	+	+	+	+	+
Radcliff (2017)	+	?	•		?	+	•	+	+	+	+	+	+
Vaccaro (2018)		?	?	?	?	+		+	+	+	+	+	+

Fig. 2 Risk bias of included studies.

TABLE 2 The heterogeneity test and meta-analysis of outcome measurements

Outcome measurements	Included studies	Participants	l ²	Statistic effect model	Effect estimate	P-value
Overall success	6	1734	0%	OR (M-H, Fixed, 95% CI)	2.10 [1.70, 2.59]	<0.00001
NDI success	6	1972	20%	OR (M-H, Fixed, 95% CI)	1.73 [1.37, 2.18]	< 0.00001
Neurological success	7	1982	16%	OR (M-H, Fixed, 95% CI)	1.65 [1.24, 2.20]	0.0006
Radiological success	3	1002	0%	OR (M-H, Fixed, 95% CI)	1.35 [0.88, 2.08]	0.17
NDI score	7	1885	68%	MD (IV, Random, 95% CI)	-2.88 [-5.93, 0.17]	0.06
VAS neck pain	5	1366	33%	MD (IV, Fixed, 95% CI)	-5.50 [-8.49, -2.52]	0.0003
VAS arm pain	4	1134	0%	MD (IV, Fixed, 95% CI)	-3.78 [-7.04, -0.53]	0.02
SF-36 PCS	4	1149	0%	MD (IV, Fixed, 95% CI)	1.93 [0.53, 3.32]	0.007
SF-36 MCS	3	761	0%	MD (IV, Fixed, 95% CI)	2.62 [0.95, 4.29]	0.002
Total reported AE	8	2872	46%	OR (M-H, Fixed, 95% CI)	1.14 [0.92, 1.42]	0.22
Serious AE	4	1756	13%	OR (M-H, Fixed, 95% CI)	0.89 [0.71, 1.11]	0.29
Device/surgery-related AE	6	2317	2%	OR (M-H, Fixed, 95% CI)	0.90 [0.68, 1.18]	0.43
Symptomatic ASD	6	1628	29%	OR (M-H, Fixed, 95% CI)	0.46 [0.34, 0.63]	<0.00001
Radiological superior ASD	2	659	83%	OR (M-H, Random, 95% CI)	0.63 [0.28, 1.43]	0.27
Radiological inferior ASD	2	474	78%	OR (M-H, Random, 95% CI)	0.45 [0.19, 1.11]	0.08
Total secondary surgery	8	2058	64%	OR (M-H, Random, 95% CI)	0.50 [0.29, 0.87]	0.01
Secondary surgery at the index level	8	2712	55%	OR (M-H, Random, 95% CI)	0.46 [0.29, 0.74]	0.001
Secondary surgery at the adjacent level	9	2937	18%	OR (M-H, Fixed, 95% CI)	0.37 [0.28, 0.49]	<0.00001
Work status	2	622	53%	OR (M-H, Random, 95% CI)	1.33 [0.78, 2.25]	0.29
Patients' satisfaction rate	4	1224	0%	OR (M-H, Fixed, 95% CI)	2.14 [1.50, 3.05]	<0.0001
Patients' recommendation rate	2	727	0%	OR (M-H, Fixed, 95% CI)	3.23 [1.79, 5.80]	<0.0001

AE, adverse event; ASD, adjacent segment degeneration; CI, confidence interval; MD, mean difference; NDI, neck disability index; OR, odds ratio; VAS, visual analog score.

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heterogeneity. Therefore, a random effects model could be applied for combined statistics. The results of the heterogeneity test are summarized in Table 2.

Results of the Meta-Analysis

We pooled all extracted data comparing CDA with ACDF for CDD in this meta-analysis. The combined results are shown in Table 2 and Figs 3–8.

For clinical success rate, CDA showed significant superiority in overall success (OR = 2.10, 95% CI [1.70, 2.59], P < 0.00001, Fig. 3A), NDI success (OR = 1.73, 95% CI [1.37, 2.18], P < 0.00001; Fig. 3B), and neurological success (OR = 1.65, 95% CI [1.24, 2.20], P = 0.0006; Fig. 3C), while

no superiority was found in radiological success (OR = 1.35, 95% *CI* [0.88, 2.08], P = 0.17; Fig. 3D).

Functional outcome measurements showed superiority in CDA except for NDI score. The NDI score (*WMD* = -2.88, 95% *CI* [-5.93, 0.17]), *P* = 0.06; Fig. 4A) was found to be lower in CDA without statistical difference. However, the combined results that favored CDA were identified in neck pain score (*WMD* = -5.50, 95% *CI* [-8.49, -2.52], *P* = 0.0003; Fig. 4B), arm pain score (*WMD* = -3.78, 95% *CI* [-7.04, -0.53], *P* = 0.02; Fig. 4C), SF-36 PCS (*WMD* = 1.93, 95% *CI* [0.53, 3.32], *P* = 0.0007; Fig. 4D), and SF-36 MCS (*WMD* = 2.62, 95% *CI* [0.95, 4.29], *P* = 0.002; Fig. 4E).

No superiority was showed in AE. Total reported AE (OR = 1.14, 95% *CI* [0.92, 1.42], P = 0.22, Fig. 5A), serious

				-			• ••••••
Study or subgroup	CD/ Evente	A Total	ACDI	Total	Weight	Odds ratio	Odds ratio M_H Eixed 95% Cl
Burkus (2014)	Lvents	010	110	100		171 [1 11 0 69]	
Coric (2014)	71	92	48	83	20.0%	2 47 [128 4 74]	
Gornet (2019)	119	148	74	119	13.4%	2 50 [1 44 4 32]	
Lavelle (2018)	104	128	69	104	11.9%	2.20 [1.20, 4.01]	
Radcliff (2017a)	64	116	25	50	13.1%	1.23 [0.63, 2.39]	
Radcliff (2017b)	104	171	27	78	12.1%	2.93 [1.68, 5.13]	
Vaccaro (2018)	103	130	77	121	13.8%	2.18 [1.24, 3.83]	
Total (95% CI)		997		737	100.0%	2.10 [1.70, 2.59]	•
Total events	724		436				
Hetetrogeneity: $\chi^2 = 5$.38, df = 6	(P = 0.	$(.50); I^2 = 0$)%		0 15	
Test for overall effects	s: Z = 6.89	(<i>P</i> < 0.	00001)			0.05	
	CD/	4	ACD	-		Odds ratio	Odds ratio
Study or subgroup	Events	Total	Events	Total	Weight	M–H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Burkus (2014)	176	211	145	181	24.3%	1.25 [0.75, 2.09]	
Gornet (2019)	130	147	88	115	10.7%	2.35 [1.21, 4.56]	
Lavelle (2018)	114	126	78	103	7.7%	3.04 [1.44, 6.42]	
Phillips (2015)	128	160	89	128	18.6%	1.75 [1.02, 3.01]	
Radcliff (2017a)	137	162	67	79	13.1%	0.98 [0.46, 2.07]	
Radcliff (2017b)	187	224	73	104	15.5%	2.15 [1.24, 3.71]	
Vaccaro (2018)	111	125	90	107	10.2%	1.50 [0.70, 3.20]	
Total (95% CI)		1155		817	100.0%	1 73 [1 37 2 18]	
Total events	983		630	011	100.070		•
Hetetrogeneity: v ² – 7	'50 df - 6	(P - 0)	28)· /² – 2	0%		-	
Test for overall effects	z = 4.60	(P < 0.	00001)	0,0		0.05	0.2 1 5 20
			,				Favore [CDA] Favore [ACDE]
	CD4	<u>`</u>	ACD	-		Odds ratio	Odds ratio
Study or subgroup	CD/ Events	A Total	ACDI Events	= Total	Weight	Odds ratio M–H, Fixed, 95% Cl	Odds ratio M-H, Fixed, 95% Cl
Study or subgroup	CDA Events 187	A Total 212	ACDI Events 145	= Total 182	Weight 25.6%	Odds ratio M–H, Fixed, 95% Cl 1.91 [1.10, 3.31]	Odds ratio M-H, Fixed, 95% Cl
Study or subgroup Burkus (2014) Gornet (2019)	CD/ Events 187 137	Total 212 148	ACDI Events 145 99	Total 182 115	Weight 25.6% 11.5%	Odds ratio M–H, Fixed, 95% Cl 1.91 [1.10, 3.31] 2.01 [0.90, 4.52]	Odds ratio M-H, Fixed, 95% Cl
Study or subgroup Burkus (2014) Gornet (2019) Janssen (2015)	CD4 Events 187 137 64	A Total 212 148 73	ACDI Events 145 99 56	Total 182 115 63	Weight 25.6% 11.5% 10.3%	Odds ratio M–H, Fixed, 95% Cl 1.91 [1.10, 3.31] 2.01 [0.90, 4.52] 0.89 [0.31, 2.54]	Odds ratio M-H, Fixed, 95% Cl
Study or subgroup Burkus (2014) Gornet (2019) Janssen (2015) Lavelle (2018)	CDA Events 187 137 64 116	A Total 212 148 73 126	ACDI Events 145 99 56 98	Total 182 115 63 103	Weight 25.6% 11.5% 10.3% 11.9%	Odds ratio M-H, Fixed, 95% Cl 1.91 [1.10, 3.31] 2.01 [0.90, 4.52] 0.89 [0.31, 2.54] 0.59 [0.20, 1.79]	Odds ratio M-H, Fixed, 95% Cl
Study or subgroup Burkus (2014) Gornet (2019) Janssen (2015) Lavelle (2018) Phillips (2015)	CDA Events 187 137 64 116 146	Total 212 148 73 126 158	ACDI Events 145 99 56 98 112	Total 182 115 63 103 128	Weight 25.6% 11.5% 10.3% 11.9% 13.1%	Odds ratio M-H, Fixed, 95% Cl 1.91 [1.10, 3.31] 2.01 [0.90, 4.52] 0.89 [0.31, 2.54] 0.59 [0.20, 1.79] 1.74 [0.79, 3.82]	Odds ratio M-H, Fixed, 95% Cl
Study or subgroup Burkus (2014) Gornet (2019) Janssen (2015) Lavelle (2018) Phillips (2015) Radcliff (2017a)	CDA Events 187 137 64 116 146 109	Total 212 148 73 126 158 123	ACDI Events 145 99 56 98 112 46	Total 182 115 63 103 128 52	Weight 25.6% 11.5% 10.3% 11.9% 13.1% 10.2%	Odds ratio M–H, Fixed, 95% Cl 1.91 [1.10, 3.31] 2.01 [0.90, 4.52] 0.89 [0.31, 2.54] 0.59 [0.20, 1.79] 1.74 [0.79, 3.82] 1.02 [0.37, 2.81]	Odds ratio M-H, Fixed, 95% Cl
Study or subgroup Burkus (2014) Gornet (2019) Janssen (2015) Lavelle (2018) Phillips (2015) Radcliff (2017a) Radcliff (2017a)	CD/ Events 187 137 64 116 146 109 176	Total 212 148 73 126 158 123 188	ACDI Events 145 99 56 98 112 46 68	Total 182 115 63 103 128 52 82	Weight 25.6% 11.5% 10.3% 11.9% 13.1% 10.2% 8.4%	Odds ratio M-H, Fixed, 95% Cl 1.91 [1.10, 3.31] 2.01 [0.90, 4.52] 0.89 [0.31, 2.54] 0.59 [0.20, 1.79] 1.74 [0.79, 3.82] 1.02 [0.37, 2.81] 3.02 [1.33, 6.86] 0.00 [1.33, 6.86]	Odds ratio M-H, Fixed, 95% Cl
Study or subgroup Burkus (2014) Gornet (2019) Janssen (2015) Lavelle (2018) Phillips (2015) Radcliff (2017a) Radcliff (2017b) Vaccaro (2018)	CD/ Events 187 137 64 116 146 146 109 176 116	Total 212 148 73 126 158 123 188 124	ACDI Events 145 99 56 98 112 46 68 92	Total 182 115 63 103 128 52 82 105	Weight 25.6% 11.5% 10.3% 13.1% 10.2% 8.4% 8.9%	Odds ratio M-H, Fixed, 95% Cl 1.91 [1.10, 3.31] 2.01 [0.90, 4.52] 0.89 [0.31, 2.54] 0.59 [0.20, 1.79] 1.74 [0.79, 3.82] 1.02 [0.37, 2.81] 3.02 [1.33, 6.86] 2.05 [0.81, 5.15]	Odds ratio M-H, Fixed, 95% Cl
Study or subgroup Burkus (2014) Gornet (2019) Janssen (2015) Lavelle (2018) Phillips (2015) Radcliff (2017a) Radcliff (2017b) Vaccaro (2018)	CD/ Events 187 137 64 116 146 109 176 116	Total 212 148 73 126 158 123 188 124 1152	ACDI Events 145 99 56 98 112 46 68 92	Total 182 115 63 103 128 52 82 105 830	Weight 25.6% 11.5% 10.3% 13.1% 10.2% 8.4% 8.9%	Odds ratio M-H, Fixed, 95% Cl 1.91 [1.10, 3.31] 2.01 [0.90, 4.52] 0.89 [0.31, 2.54] 0.59 [0.20, 1.79] 1.74 [0.79, 3.82] 1.02 [0.37, 2.81] 3.02 [1.33, 6.86] 2.05 [0.81, 5.15] 165 [124, 2.20]	Odds ratio M-H, Fixed, 95% Cl
Study or subgroup Burkus (2014) Gornet (2019) Janssen (2015) Lavelle (2018) Phillips (2015) Radcliff (2017a) Radcliff (2017b) Vaccaro (2018) Total (95% CI)	CDA Events 187 137 64 116 146 109 176 116	Total 212 148 73 126 158 123 188 124 1152	ACDI Events 145 99 56 98 8112 46 68 92	Total 182 115 63 103 128 52 82 105 830	Weight 25.6% 11.5% 10.3% 11.9% 13.1% 10.2% 8.4% 8.9% 100.0%	Odds ratio M-H, Fixed, 95% Cl 1.91 [1.10, 3.31] 2.01 [0.90, 4.52] 0.89 [0.31, 2.54] 0.59 [0.20, 1.79] 1.74 [0.79, 3.82] 1.02 [0.37, 2.81] 3.02 [1.33, 6.86] 2.05 [0.81, 5.15] 1.65 [1.24, 2.20]	Odds ratio M-H, Fixed, 95% Cl
Study or subgroup Burkus (2014) Gornet (2019) Janssen (2015) Lavelle (2015) Radcliff (2017a) Radcliff (2017a) Radcliff (2017b) Vaccaro (2018) Total (95% CI) Total events Hetetrongenity: x ² = 8	CD/ Events 187 137 64 116 146 146 109 176 116	Total 212 148 73 126 158 123 188 124 1152	ACDI <u>Events</u> 145 99 56 98 112 46 68 92 716 31): <i>P</i> = 1	Total 182 115 63 103 128 52 82 105 830	Weight 25.6% 11.5% 10.3% 11.9% 13.1% 10.2% 8.4% 8.9% 100.0%	Odds ratio M-H, Fixed, 95% Cl 1.91 [1.10, 3.31] 2.01 [0.90, 4.52] 0.89 [0.31, 2.54] 0.59 [0.20, 1.79] 1.74 [0.79, 3.62] 1.02 [0.37, 2.81] 3.02 [1.33, 6.86] 2.05 [0.81, 5.15] 1.65 [1.24, 2.20]	Odds ratio M-H, Fixed, 95% Cl
Study or subgroup Burkus (2014) Gornet (2019) Janssen (2015) Lavelle (2018) Phillips (2015) Radcliff (2017a) Radcliff (2017b) Vaccaro (2018) Total (95% Cl) Total events Hetetrogeneity: $\chi^2 = 8$ Test for overall effects	CD/ Events 187 137 64 116 146 146 109 176 116 116 1.32, df = 7 ; Z = 3.43	Total 212 148 73 126 158 123 188 124 1152 (<i>P</i> = 0. (<i>P</i> < 0.)	ACDI <u>Events</u> 145 99 56 98 112 46 68 92 716 31); <i>f</i> ² = 1 0006)	Total 182 115 63 103 128 52 82 105 830 6%	Weight 25.6% 11.5% 10.3% 13.1% 10.2% 8.4% 8.9% 100.0%	Odds ratio M-H, Fixed, 95% Cl 1.91 [1.10, 3.31] 2.01 [0.90, 4.52] 0.89 [0.31, 2.54] 0.59 [0.20, 1.79] 1.74 [0.79, 3.82] 1.02 [0.37, 2.81] 3.02 [1.33, 6.86] 2.05 [0.81, 5.15] 1.65 [1.24, 2.20]	Odds ratio M-H, Fixed, 95% Cl
Study or subgroup Burkus (2014) Gornet (2019) Janssen (2015) Lavelle (2018) Phillips (20175) Radcliff (2017a) Radcliff (2017b) Vaccaro (2018) Total (95% CI) Total events Hetetrogeneity: $\chi^2 = 8$ Test for overall effects	CD/ Events 187 137 64 146 109 176 116 1051 .32, df = 7 5: Z = 3.43	Total 212 148 73 126 158 123 188 124 1152 (<i>P</i> = 0. (<i>P</i> < 0.)	ACDI Events 145 99 56 98 112 46 68 92 716 (31); <i>I</i> ² = 1 0006)	Total 182 115 63 103 128 52 82 105 830 6%	Weight 25.6% 11.5% 10.3% 13.1% 10.2% 8.4% 8.9% 100.0%	Odds ratio M-H, Fixed, 95% Cl 1.91 [1.10, 3.31] 2.01 [0.90, 4.52] 0.89 [0.31, 2.54] 0.59 [0.20, 1.79] 1.74 [0.79, 3.82] 1.02 [0.37, 2.81] 3.02 [1.33, 6.86] 2.05 [0.81, 5.15] 1.65 [1.24, 2.20] ↓ 0.05	Odds ratio M-H, Fixed, 95% Cl
Study or subgroup Burkus (2014) Gornet (2019) Janssen (2015) Laveile (2018) Phillips (2015) Radcliff (2017a) Radcliff (2017b) Vaccaro (2018) Total (95% CI) Total events Hetetrogentity: $\chi^2 = 8$ Test for overall effects	CD/ Events 187 137 64 116 146 109 176 116 116 1051 :32, df = 7 : Z = 3.43	Total 212 148 73 126 158 123 188 124 1152 (<i>P</i> = 0. (<i>P</i> < 0.)	ACDI Events 145 99 56 98 112 46 68 92 716 (31); <i>I</i> ² = 1 0006)	Total 182 115 63 103 128 52 82 105 830 6%	Weight 25.6% 11.5% 10.3% 13.1% 10.2% 8.4% 8.9% 100.0%	Odds ratio M-H, Fixed, 95% Cl 1.91 [1.10, 3.31] 2.01 [0.90, 4.52] 0.89 [0.31, 2.54] 0.59 [0.20, 1.79] 1.74 [0.79, 3.82] 1.02 [0.37, 2.81] 3.02 [1.33, 6.86] 2.05 [0.81, 5.15] 1.65 [1.24, 2.20] ↓ 0.05	Odds ratio M-H, Fixed, 95% CI
Study or subgroup Burkus (2014) Gornet (2019) Janssen (2015) Lavelle (2018) Phillips (2015) Radcliff (2017a) Radcliff (2017b) Vaccaro (2018) Total (95% CI) Total events Hetetrogeneity: $\chi^2 = 8$ Test for overall effects	CD/ Events 187 137 64 116 146 109 176 116 1051 1.32, df = 7 5; Z = 3.43	Total 212 148 73 126 158 123 188 124 1152 (<i>P</i> = 0. (<i>P</i> < 0.)	ACDI Events 145 99 56 98 112 46 68 92 716 (31); <i>f</i> ² = 1 0006)	Total 182 115 63 103 128 52 82 105 830 6%	Weight 25.6% 11.5% 10.3% 13.1% 10.2% 8.4% 8.9% 100.0%	Odds ratio M-H, Fixed, 95% Cl 1.91 [1.10, 3.31] 2.01 [0.90, 4.52] 0.89 [0.31, 2.54] 0.59 [0.20, 1.79] 1.74 [0.79, 3.82] 1.02 [0.37, 2.81] 3.02 [1.33, 6.86] 2.05 [0.81, 5.15] 1.65 [1.24, 2.20] 	Odds ratio M-H, Fixed, 95% Cl 0.2 1 5 20 Favors [CDA] Favors [ACDF]
Study or subgroup Burkus (2014) Gornet (2019) Janssen (2015) Lavelle (2018) Phillips (2017a) Radcliff (2017a) Radcliff (2017b) Vaccaro (2018) Total (95% CI) Total events Hetetrogeneity: $\chi^2 = 8$ Test for overall effects	CD/ Events 187 137 64 116 146 109 176 116 1051 :.32, df = 7 :: Z = 3.43 CD/ Events	Total 212 148 73 126 158 123 188 124 1152 (P = 0. (P < 0.	ACDI Events 145 99 56 98 112 46 68 92 716 (31); <i>I²</i> = 1 0006) ACDI Events	Total 182 115 63 103 128 52 82 105 830 6%	Weight 25.6% 11.5% 10.3% 13.1% 10.2% 8.4% 8.9% 100.0% Weight	Odds ratio M-H, Fixed, 95% Cl 1.91 [1.10, 3.31] 2.01 [0.90, 4.52] 0.89 [0.31, 2.54] 0.59 [0.20, 1.79] 1.74 [0.79, 3.82] 1.02 [0.37, 2.81] 3.02 [1.33, 6.86] 2.05 [0.81, 5.15] 1.65 [1.24, 2.20] Cdds ratio M-H, Fixed, 95% Cl	Odds ratio M-H, Fixed, 95% Cl
Study or subgroup Burkus (2014) Gornet (2019) Janssen (2015) Lavelle (2018) Phillips (2015) Radcliff (2017a) Radcliff (2017b) Vaccaro (2018) Total (95% CI) Total events Hetetrogeneity: $\chi^2 = 8$ Test for overall effects Study or subgroup Gornet (2019)	CD/ Events 187 137 64 116 146 109 176 116 1051 1.32, df = 7 5; Z = 3.43 CD/ Events 138	Total 212 148 73 126 158 123 188 124 1152 (P = 0. (P <	ACDI Events 145 99 56 68 98 112 46 68 92 716 31); <i>I</i> ² = 1 0006) 716 31); <i>I</i> ² = 1 0006) ACDI Events 108	Total 182 115 63 103 128 52 82 105 830 6%	Weight 25.6% 11.5% 10.3% 13.1% 10.2% 8.4% 8.9% 100.0% Weight 23.5%	Odds ratio M-H, Fixed, 95% Cl 1.91 [1.10, 3.31] 2.01 [0.90, 4.52] 0.89 [0.31, 2.54] 0.59 [0.20, 1.79] 1.74 [0.79, 3.82] 1.02 [0.37, 2.81] 3.02 [1.33, 6.86] 2.05 [0.81, 5.15] 1.65 [1.24, 2.20] Cdds ratio M-H, Fixed, 95% Cl 1.28 [0.51, 3.18]	Odds ratio M-H, Fixed, 95% Cl 0.2 1 5 20 Favors [CDA] Favors [ACDF] © Odds ratio M-H, Fixed, 95% Cl
Study or subgroup Burkus (2014) Gornet (2019) Janssen (2015) Lavelle (2018) Phillips (2015) Radcliff (2017a) Radcliff (2017b) Vaccaro (2018) Total (95% CI) Total events Hetetrogeneity: $\chi^2 = 8$ Test for overall effects Study or subgroup Gornet (2019) Phillips (2015)	CD/ Events 187 137 64 116 146 109 176 116 1051 1.32, df = 7 5: Z = 3.43 CD/ Events 138 146	Total 212 148 73 126 158 123 188 124 1152 (<i>P</i> = 0. (<i>P</i> < 0. (<i>P</i> < 0. A Total 148 158	ACDI Events 145 99 56 68 98 112 46 68 92 716 (31); <i>I</i> ² = 1 0006) ACDI Events 108 112	Total 182 115 63 103 128 82 105 830 6% Total 118 128 128	Weight 25.6% 11.5% 10.3% 13.1% 10.2% 8.4% 100.0% Weight 23.5% 272%	Odds ratio M-H, Fixed, 95% Cl 1.91 [1.10, 3.31] 2.01 [0.90, 4.52] 0.89 [0.31, 2.54] 0.59 [0.20, 1.79] 1.74 [0.79, 3.82] 1.02 [0.37, 2.81] 3.02 [1.33, 6.86] 2.05 [0.81, 5.15] 1.65 [1.24, 2.20] ↓ 0.05 Odds ratio M-H, Fixed, 95% Cl 1.28 [0.51, 3.18] 1.74 [0.79, 3.82]	Odds ratio M-H, Fixed, 95% Cl 0.2 1 5 20 Favors [CDA] Favors [ACDF] Odds ratio M-H, Fixed, 95% Cl Odds ratio
Study or subgroup Burkus (2014) Gornet (2019) Janssen (2015) Lavelle (2018) Phillips (2015) Radcliff (2017a) Radcliff (2017b) Vaccaro (2018) Total (95% CI) Total events Hetetrogeneity: $\chi^2 = 8$ Test for overall effects Study or subgroup Gornet (2019) Phillips (2015) Radcliff (2017a)	CD/ Events 187 64 116 146 109 176 116 132, df = 7 5: Z = 3.43 CD/ Events 138 146 113	Total Total 212 148 73 126 158 123 188 124 1152 (P = 0. (P < 0. (ACDI Events 145 99 56 98 112 46 68 92 716 (31); <i>f</i> = 1 0006) 716 (31); <i>f</i> = 1 0006) ACDI Events 108 112 49	Total 182 115 63 103 128 52 82 105 830 66%	Weight 25.6% 11.5% 10.3% 11.9% 13.1% 10.2% 8.4% 8.9% 100.0% Weight 23.5% 27.2% 20.0%	Odds ratio M-H, Fixed, 95% Cl 1.91 [1.10, 3.31] 2.01 [0.90, 4.52] 0.89 [0.31, 2.54] 0.59 [0.20, 1.79] 1.74 [0.79, 3.82] 1.02 [0.37, 2.81] 3.02 [1.33, 6.86] 2.05 [0.81, 5.15] 1.65 [1.24, 2.20] ↓ 0.05 Odds ratio M-H, Fixed, 95% Cl 1.28 [0.51, 3.18] 1.74 [0.79, 3.82] 1.60 [0.64, 3.89]	Odds ratio M-H, Fixed, 95% Cl 0.2 1 5 20 Favors [CDA] Favors [ACDF] © Odds ratio M-H, Fixed, 95% Cl
Study or subgroup Burkus (2014) Gornet (2019) Janssen (2015) Lavelle (2018) Phillips (2017a) Radcliff (2017b) Vaccaro (2018) Total (95% CI) Total events Heterogeneity: $\chi^2 = 8$ Test for overall effects Study or subgroup Gornet (2019) Phillips (2017a) Radcliff (2017a)	CD/ Events 187 137 64 116 146 109 176 116 1051 3.32, df = 7 5.2 = 3.43 CD/ Events 138 146 113 169	Total 212 148 73 126 158 123 188 124 1152 (P = 0.) (P < 0.) 4 Total 148 158 126 188 188 188 188 188 188 188 18	ACDI Events 145 99 56 68 98 112 46 68 92 716 31); <i>f</i> = 1 0006) ACDI Events 108 112 49 71	- Total 182 115 63 103 128 52 82 105 830 6% - Total 118 128 58 830 6%	Weight 25.6% 11.5% 10.3% 11.9% 31.1% 10.2% 8.4% 8.9% 100.0% Weight 23.5% 27.2% 29.3%	Odds ratio M-H, Fixed, 95% Cl 1.91 [1.10, 3.31] 2.01 [0.90, 4.52] 0.89 [0.31, 2.54] 0.59 [0.20, 1.79] 1.74 [0.79, 3.82] 1.02 [1.33, 6.86] 2.05 [0.81, 5.15] 1.65 [1.24, 2.20] M-H, Fixed, 95% Cl 1.28 [0.51, 3.18] 1.74 [0.79, 3.82] 1.60 [0.64, 3.98] 0.88 [0.35, 2.18]	Odds ratio M-H, Fixed, 95% Cl 0.2 1 5 20 Favors [CDA] Favors [ACDF] © Odds ratio M-H, Fixed, 95% Cl
Study or subgroup Burkus (2014) Gornet (2019) Janssen (2015) Lavelle (2018) Phillips (2017a) Radcliff (2017a) Radcliff (2017b) Vaccaro (2018) Total (95% CI) Total events Hetetrogeneity: $\chi^2 = 8$ Test for overall effects Study or subgroup Gornet (2019) Phillips (2015) Radcliff (2017a) Radcliff (2017b)	CD/ Events 187 137 64 116 146 109 176 116 1051 1.32, df = 7 5: Z = 3.43 CD/ Events 138 146 113 169	A Total 212 148 73 126 158 123 188 124 1152 (P = 0. (P < 0. (P < 0. A Total 148 158 124 126 126 128 128 128 129 126 128 128 129 129 129 129 129 129 129 129	ACDI Events 145 99 56 68 92 716 31); <i>P</i> = 1 0006) ACDI Events 108 112 49 71	- Total 182 115 63 103 128 52 82 105 830 6% - - - - - - - - - - - - -	Weight 25.6% 11.5% 10.3% 11.9% 13.1% 10.2% 8.4% 8.9% 100.0% Weight 23.5% 27.2% 20.0% 29.3%	Odds ratio M-H, Fixed, 95% Cl 1.91 [1.10, 3.31] 2.01 [0.90, 4.52] 0.89 [0.31, 2.54] 0.59 [0.20, 1.79] 1.74 [0.79, 3.82] 1.02 [0.37, 2.81] 3.02 [1.33, 6.86] 2.05 [0.81, 5.15] 1.65 [1.24, 2.20] M-H, Fixed, 95% Cl 1.28 [0.51, 3.18] 1.74 [0.79, 3.82] 1.60 [0.64, 3.98] 0.88 [0.35, 2.18]	Odds ratio M-H, Fixed, 95% Cl 0.2 1 5 20 Favors [CDA] Favors [ACDF] Odds ratio M-H, Fixed, 95% Cl CO
Study or subgroup Burkus (2014) Gornet (2019) Janssen (2015) Lavelle (2018) Phillips (2015) Radcliff (2017a) Radcliff (2017b) Vaccaro (2018) Total (95% CI) Total events Hetetrogeneity: $\chi^2 = 8$ Test for overall effects Study or subgroup Gornet (2015) Radcliff (2017a) Radcliff (2017b) Total (95% CI)	CD/ Events 187 137 64 116 146 146 109 176 116 1051 1.32, df = 7 5; Z = 3.43 CD/ Events 138 146 113 169	A Total 212 148 73 126 158 123 188 124 1152 (P = 0. (P < 0. (P < 0. A Total 148 158 124 158 124 182 182 182 184 182 184 182 184 185 182 182 182 182 182 182 182 182	ACDI Events 145 99 56 68 92 716 68 92 716 (31); <i>I</i> ² = 1 0006) ACDI Events 108 112 49 71	- Total 182 115 63 103 128 52 82 105 830 6% - - - - - - - - - - - - -	Weight 25.6% 11.5% 10.3% 11.9% 13.1% 10.2% 100.0%	Odds ratio M-H, Fixed, 95% Cl 1.91 [1.10, 3.31] 2.01 [0.90, 4.52] 0.89 [0.31, 2.54] 0.59 [0.20, 1.79] 1.74 [0.79, 3.82] 1.02 [0.37, 2.81] 3.02 [1.33, 6.86] 2.05 [0.81, 5.15] 1.65 [1.24, 2.20] ↓ 0.05 Odds ratio M-H, Fixed, 95% Cl 1.28 [0.51, 3.18] 1.74 [0.79, 3.82] 1.60 [0.64, 3.98] 0.88 [0.35, 2.18] 1.35 [0.88, 2.08]	Odds ratio M-H, Fixed, 95% Cl 0.2 1 5 20 Favors [CDA] Favors [ACDF] Odds ratio M-H, Fixed, 95% Cl Generational Statements of the statement of the statem
Study or subgroup Burkus (2014) Gornet (2019) Janssen (2015) Lavelle (2018) Phillips (2015) Radcliff (2017a) Radcliff (2017a) Radcliff (2017b) Vaccaro (2018) Total (95% CI) Total events Hetetrogeneity: $\chi^2 = 8$ Test for overall effects Study or subgroup Gornet (2019) Phillips (2015) Radcliff (2017a) Radcliff (2017b) Total (95% CI) Total events	CD/ Events 187 64 116 146 146 146 146 132, df = 7 5: Z = 3.43 CD/ Events 138 146 113 169	Total 212 148 73 126 158 123 188 124 1152 ($P = 0.$ ($P < 0.$ Total 148 158 124 Total 148 158 124 Colored 188 124 Colored 188 124 Colored 188 124 Colored 188 124 Colored 188 124 Colored 188 124 Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored	ACDI Events 145 99 56 88 112 46 68 92 716 (31); <i>f</i> = 1 0006) ACDI Events 108 112 49 71	Total 182 115 63 103 128 52 822 105 830 6% Total 118 128 58 78 382 382	Weight 25.6% 11.5% 10.3% 11.9% 3.1% 10.2% 8.4% 8.9% 100.0% Weight 23.5% 27.2% 20.0% 29.3% 100.0%	Odds ratio M-H, Fixed, 95% Cl 1.91 [1.10, 3.31] 2.01 [0.90, 4.52] 0.89 [0.31, 2.54] 0.59 [0.20, 1.79] 1.72 [0.37, 2.81] 3.02 [1.33, 6.86] 2.05 [0.81, 5.15] 1.65 [1.24, 2.20] ↓ 0.05 Odds ratio M-H, Fixed, 95% Cl 1.28 [0.51, 3.18] 1.74 [0.79, 3.82] 1.60 [0.64, 3.88] 0.88 [0.35, 2.18] 1.35 [0.88, 2.08]	Odds ratio M-H, Fixed, 95% Cl 0.2 1 5 20 Favors [CDA] Favors [ACDF] © Odds ratio M-H, Fixed, 95% Cl
Study or subgroup Burkus (2014) Gornet (2019) Janssen (2015) Lavelle (2018) Phillips (2017a) Radcliff (2017a) Radcliff (2017b) Vaccaro (2018) Total (95% CI) Total events Hetetrogeneity: $\chi^2 = 8$ Test for overall effects Study or subgroup Gornet (2019) Phillips (2017a) Radcliff (2017a) Radcliff (2017a) Radcliff (2017b) Total events Hetetrogeneity: $\chi^2 = 1$	CD/ Events 187 137 64 116 146 109 176 116 1051 32, df = 7 3: Z = 3.43 CD/ Events 138 146 113 169 566 .40, df = 3	Total 212 148 73 126 158 123 188 124 1152 ($P = 0(P < 0)$ Total 148 158 126 148 158 126 6 6 6 6 6 6 7 7 7 7 7 7 7 7	ACDI Events 145 99 56 68 98 112 46 68 92 716 31); <i>f</i> = 1 0006) ACDI Events 108 112 49 71 340 70; <i>f</i> = 0	Total 182 115 63 103 128 52 205 830 6% 6% Total 118 128 830 6% Total 118 128 830 6%	Weight 25.6% 11.5% 10.3% 11.9% 31.1% 10.2% 8.4% 8.9% 100.0% Weight 23.5% 27.2% 29.3% 100.0%	Odds ratio M-H, Fixed, 95% Cl 1.91 [1.10, 3.31] 2.01 [0.90, 4.52] 0.89 [0.31, 2.54] 0.59 [0.20, 1.79] 1.74 [0.79, 3.82] 1.02 [0.37, 2.81] 3.02 [1.33, 6.86] 2.05 [0.81, 5.15] 1.65 [1.24, 2.20] ↓ Odds ratio M-H, Fixed, 95% Cl 1.28 [0.51, 3.18] 1.74 [0.79, 3.82] 1.60 [0.64, 3.98] 0.88 [0.35, 2.18] 1.35 [0.88, 2.08]	Odds ratio M-H, Fixed, 95% Cl 0.2 Favors [CDA] Odds ratio M-H, Fixed, 95% Cl Odds ratio M-H, Fixed, 95% Cl Odds ratio M-H, Fixed, 95% Cl 0.2 0.2 0.2 0.2 0.2 0.2 0.2 0.2
Study or subgroup Burkus (2014) Gornet (2019) Janssen (2015) Lavelle (2018) Phillips (2015) Radcliff (2017a) Radcliff (2017b) Vaccaro (2018) Total (95% CI) Total events Hetetrogeneity: $\chi^2 = 8$ Test for overall effects Study or subgroup Gornet (2019) Phillips (2015) Radcliff (2017a) Radcliff (2017b) Total (95% CI) Total events Hetetrogeneity: $\chi^2 = 1$ Total (95% CI) Total events Hetetrogeneity: $\chi^2 = 1$ Total events Hetetrogeneity: $\chi^2 = 1$ Test for overall effects	CD/ Events 187 137 64 116 146 109 176 116 1051 1.32, df = 7 5: Z = 3.43 CD/ Events 138 146 113 169 566 6.40, df = 3 5: Z = 1.36	$\begin{array}{c} \mathbf{A} \\ \hline \mathbf{Total} \\ 212 \\ 148 \\ 73 \\ 126 \\ 158 \\ 123 \\ 123 \\ 123 \\ 123 \\ 124 \\ 1152 \\ (P=0. \\ (P=0. \\ P=0. \\ (P=0. \\ P=0. \\ P=0. \\ \end{array}$	ACDI Events 145 99 56 68 98 112 46 68 92 716 31); <i>I</i> ² = 1 0006) ACDI Events 108 112 49 71 340 70); <i>I</i> ² = 0	Total 182 115 3 103 128 82 105 830 6% Total 118 128 58 78 382 382	Weight 25.6% 11.5% 10.3% 11.9% 13.1% 10.2% 8.4% 8.9% 100.0% Weight 23.5% 27.2% 20.0% 29.3% 100.0%	Odds ratio M-H, Fixed, 95% Cl 1.91 [1.10, 3.31] 2.01 [0.90, 4.52] 0.89 [0.31, 2.54] 0.59 [0.20, 1.79] 1.74 [0.79, 3.82] 1.02 [0.37, 2.81] 3.02 [1.33, 6.86] 2.05 [0.81, 5.15] 1.65 [1.24, 2.20] M-H, Fixed, 95% Cl 1.28 [0.51, 3.18] 1.74 [0.79, 3.82] 1.60 [0.64, 3.98] 0.88 [0.35, 2.18] 1.35 [0.88, 2.08]	Odds ratio M-H, Fixed, 95% Cl 0.2 1 5 20 Favors [CDA] Odds ratio M-H, Fixed, 95% Cl Cl Favors [ACDF] C C Favors [CDA] Favors [ACDF] C Favors [CDA]

Fig. 3 Forest plot comparing clinical success rate between cervical disc arthroplasty (CDA) and anterior cervical discectomy and fusion (ACDF). (A) Overall success. (B) Neck disability index (NDI) success. (C) Neurological success. (D) Radiological success. *Cl*, confidence interval.

LONG-TERM RESULTS COMPARING CDA AND ACDF



Fig. 4 Forest plot comparing functional outcome measurements between cervical disc arthroplasty (CDA) and anterior cervical discectomy and fusion (ACDF). (A) Neck disability index (NDI) score. (B) Visual analog score (VAS) neck pain. (C) VAS arm pain. (D) Short Form-36 physical component score (SF-36 PCS). (E) Short Form-36 mental component score (SF-36 MCS). *CI*, confidence interval.

AE (OR = 0.89, 95% *CI* [0.71, 1.11], P = 0.29, Fig. 5B), and device/surgery-related AE (OR = 0.90, 95% *CI* [0.68, 1.18], P = 0.43; Fig. 5C) were similar between CDA and ACDF.

As for ASD, the incidence of symptomatic ASD (OR = 0.46, 95% CI [0.34, 0.63]), P < 0.00001; Fig. 6A) was significantly lower in CDA; however, radiologically superior ASD (OR = 0.63, 95% CI [0.28, 1.43], P = 0.27; Fig. 6B) and inferior ASD (OR = 0.45, 95% CI [0.19, 1.11], P = 0.08; Fig. 6C) were not significantly different between groups.

Strikingly, when compared to ACDF, our results revealed that CDA had significant superiority in total secondary surgery (OR = 0.50, 95% *CI* [0.29, 0.87], P = 0.01, Fig. 7A), secondary surgery at the index level (OR = 0.46, 95% *CI* [0.29, 0.74], P = 0.001, Fig. 7B), and secondary surgery at the adjacent level (OR = 0.37, 95% *CI* [0.28, 0.49], P < 0.00001; Fig. 7C).

Finally, work status (OR = 1.33, 95% CI [0.78, 2.25], P = 0.29, Fig. 8A) was similar at the last follow up between CDA and ACDF. CDA achieved a higher rate of patient satisfaction (OR = 2.14, 95% CI [1.50, 3.05], P = 0.0002; Fig. 8B)

LONG-TERM RESULTS COMPARING CDA AND ACDF

Study or subgroup	Ever	nts To	tal Eve	nts To	otal Weig	Odds ratio ht M-H, Fixed, 95%	CI	Odds M–H, Fixed	ratio d, 95% Cl
Burkus (2014)	2	59 2	76 2	32 2	65 9.3	% 2,17 [1.18 3	3,991		— —
Coric (2018)		61 1	36	53 1	33 18.8	1.23 [0.76.	1.991	-	
Donk (2017)		2	50	6	47 3.8	0.28 [0.05.	1.491		_
Gornet (2019)	2	06 2	09 1	79 1	88 1.7	% 3.45 [0.92, 12	.951		<u> </u>
Janssen (2015)		28 1	06	30 1	03 14.3	0.87 [0.48.	1.601		<u> </u>
Phillips (2015)		91 2	14	74 1	90 28.7	% 1.16 [0.78.	1.731	-	
Badcliff (2017a)		10 1	64	3	81 24	% 1.69 [0.45, 6	5.311		· · · · · ·
Radeliff (2017b)		12 2	25	9 1	05 7.4	% 0.60 [0.25]	1471		<u> </u>
Vaccaro (2018)	2	05 2	36 1	30 1	44 135	% 0.71 [0.37 ·	1391		<u> </u>
1400410 (2010)	-	00 2	.00 1	00 1		0.71 [0.07,	1.00]		
Total (95% CI)		16	516	12	256 100.0	% 1.14 [0.92. 1	1.421		•
Total aventa	g	74	7	, 16					·
Heterogeneity: 2 -	14 69 df -	- 8 (P -	، ۱۹۰۰ ۱۹۰۰ ۱۹۰۰	- 46%			⊢		<u> </u>
Test for overall offer	$14.00, 01 = 10^{4}$	2 (P _ 1	n 22)	= +0 /0			0.0	2 0.1	1 10 50
	515. E = 1.E	- (, - ,	0.2C)					Favors [CDA]	Favors [ACDF]
Study or subgroup	(Even	CDA Its To	A Ital Ever	ACDF	tal Weig	Oddsratio ht M-H. Fixed, 95%	6 CI	Odds M-H Fixe	s ratio
Gornet (2010)	21	24	209 4	20	188 01 0	0 82 10 EF	1 2/1		+
Bhilling (2015)	1	24 4	209 1	20	100 31.0	1% 0.03 [0.33,	1.24]		
Primps (2015)		91 2	214	74	190 27.7	% I.16[0.78,	1.73		
Radcliff (2017a)		10	107	3	81 2.3	1.69 [0.45, 6	0.31]		
Hadcliff (2017b)		12 2	225	6	105 7.1	% 0.60 [0.25,	1.47]		T
Vaccaro (2018)		87 2	236	65	144 31.3	% 0.71 [0.47, [.]	1.08]		Ť
				_					
i otal (95% CI)		10	J48		100.0	0.89 [0.71, 1	1.11]	•	1
Total events	3	24	2	271					
Heterogeneity: $\chi^2 =$	4.57, df = 4	4 (P = 0)	0.33); <i>I</i> ² =	13%			~ F	2 01	
Test for overall effect	cts: Z = 1.0	6 (<i>P</i> = 0	0.29)				0.0	∠ U.I	ı 10 50
								Favors [CDA]	Favors [ACDF]
									B
	C	DA	ACI	DF		Odds ratio		Odds ra	itio
Study or subgroup	Events	s Tota	I Events	Total	Weight	M-H, Fixed, 95% C	1	M–H, Fixed, 9	95% CI
Coric (2018)	6	1 13	6 53	133	27 /%	123 [0 76 199	1		<u> </u>
Gornet (2019)		7 20	9 14	188	13.2%	0 43 [0 17 1 09	i		
Janssen (2015)	2	, <u> </u>	3 30	100	20.0%	0.95 [0.52, 1.73	i		_
Lavelle (2018)	10	0 24	2 11	221	10.2%	0.82 [0.34, 1.98	1		_
Phillips (2015)	13	3 21	4 16	190	11.8%	0.70 [0.33, 1.50	1		_
Radcliff (2017a)	10	0 16	4 6	81	3.5%	1.69 [0.45, 6.31	1		· · · · ·
Badcliff (2017b)	12	2 22	5 6	105	10.8%	0.60 [0.25, 6.47	i		_
		-					1		
Total (95% CI)		1293	3	1024	100.0%	0.90 [0.68, 1.18]	•	
Total events	14	1	136	;			-	-	
Heterogeneity: v ² -	6 11 df - 6	6 (P - (1 41)· /2 -	2%			H		
			0.10)				Fav	vors [experimental]	Favors [control]
	CD4		ACD	F		Oddo ratio	Fav	vors [experimental]	Favors [control]
Study or subgroup	CDA	Total	ACD	F	Weight	Odds ratio	Fav	vors [experimental] Odds ra	Favors [control]
Study or subgroup	CDA Events	Total	ACD Events	F Total	Weight	Odds ratio M-H, Fixed, 95% C	Fav	vors [experimental] Odds ra M–H, Fixed, s	Favors [control]
Study or subgroup	CDA Events 0	Total	ACD Events 5	F Total 47	Weight 5.1%	Odds ratio M–H, Fixed, 95% C 0.08 [0.00, 1.42	Fav 2] ←	vors [experimental] Odds ra M–H, Fixed,	Favors [control]
Study or subgroup Jonk (2017) lanssen (2015)	CDA Events 0 1	Total 50 103	ACD Events 5 2	F Total 47 106	Weight 5.1% 1.8%	Odds ratio M–H, Fixed, 95% C 0.08 [0.00, 1.42 0.51 [0.05, 5.71	Fav 2] ←]	Vors [experimental] Odds ra M–H, Fixed, S	Favors [control] C
Study or subgroup Jonk (2017) lanssen (2015) .avelle (2018)	CDA <u>Events</u> 0 1 12	Total 50 103 124	ACD Events 5 2 160	F Total 47 106 101	Weight 5.1% 1.8% 14.4%	Odds ratio M–H, Fixed, 95% C 0.08 [0.00, 1.42 0.51 [0.05, 5.71 0.57 [0.26, 1.27	Fav 2] ← 1]	Odds ra M–H, Fixed, 9	Favors [control] C
Study or subgroup Donk (2017) lanssen (2015) .avelle (2018) MacDowall (2019)	CDA Events 0 1 12 21	Total 50 103 124 67	ACD <u>Events</u> 5 2 160 150	F Total 47 106 101 51	Weight 5.1% 1.8% 14.4% 10.6%	Odds ratio M-H, Fixed, 95% C 0.08 [0.00, 1.42 0.51 [0.05, 5.71 0.57 [0.26, 1.27 1.10 [0.50, 2.42	Fav [] ←] [] []	Odds ra M-H, Fixed, S	Favors [control] C
Study or subgroup Donk (2017) lanssen (2015) .avelle (2018) MacDowall (2019) ladeliff (2017a)	CDA Events 0 1 12 21 4	Total 50 103 124 67 164	ACD Events 5 2 160 150 8	F Total 47 106 101 51 105	Weight 5.1% 1.8% 14.4% 10.6% 8.6%	Odds ratio M–H, Fixed, 95% C 0.88 [0.00, 1.42 0.51 [0.05, 5.71 0.57 [0.26, 1.27 1.10 [0.50, 2.42 0.30 [0.09, 1.03	Fav [] ←]] [] [] []	Odds ra M–H, Fixed, S	Favors [control] C
Study or subgroup Donk (2017) lanssen (2015) .avelle (2018) MacDowall (2019) Badcliff (2017a) Tadcliff (2017b)	CDA Events 0 1 12 21 4 10	Total 50 103 124 67 164 225	ACD Events 2 160 150 8 8	F Total 47 106 101 51 105 105	Weight 5.1% 1.8% 14.4% 10.6% 8.6% 9.4%	Odds ratio M-H, Fixed, 95% C 0.08 [0.00, 1.42 0.51 [0.05, 5.71 1.10 [0.50, 2.42 0.30 [0.09, 1.03 0.56 [0.22, 1.47	Fav	Vors [experimental] Odds ra M–H, Fixed, 9	Favors [control]
Study or subgroup Donk (2017) lanssen (2015) .avelle (2018) MacDowall (2019) ladcliff (2017a) Padcliff (2017b) /accaro (2018)	CDA <u>Events</u> 0 1 12 21 4 10 40	Total 50 103 124 67 164 225 263	ACD Events 5 2 160 150 8 8 54	F Total 47 106 101 51 105 105 144	Weight 5.1% 1.8% 14.4% 10.6% 8.6% 9.4% 50.3%	Odds ratio M-H, Fixed, 95% C 0.08 [0.00, 1.42 0.51 [0.05, 5.7] 1.10 [0.50, 2.42 0.30 [0.09, 1.03 0.56 [0.22, 1.47 0.34 [0.21, 0.55	Fav	Odds ra M-H, Fixed,	Favors [control]
Study or subgroup Donk (2017) Lanssen (2015) Lavelle (2018) MacDowall (2019) Radoliff (2017a) Radoliff (2017b) /accaro (2018)	CDA Events 0 1 12 21 4 10 40	Total 50 103 124 67 164 225 263	ACD Events 5 2 160 150 8 8 5 4	F Total 47 106 101 51 105 105 144	Weight 5.1% 1.8% 14.4% 10.6% 8.6% 9.4% 50.3%	Odds ratio M–H, Fixed, 95% C 0.08 [0.00, 1.42 0.51 [0.05, 5.71 0.57 [0.26, 1.27 1.10 [0.50, 2.42 0.30 [0.09, 1.03 0.56 [0.22, 1.47 0.34 [0.21, 0.55	Fav	Odds ra M-H, Fixed, 9	Favors [control] C
Study or subgroup Donk (2017) lanssen (2015) .avelle (2018) MacDowall (2019) Hadcliff (2017a) Hadcliff (2017b) Vaccaro (2018) Total (95% CI)	CDA Events 0 1 12 21 4 10 40	Total 50 103 124 67 164 225 263 969	ACD <u>Events</u> 5 2 160 150 8 8 54	F Total 47 106 101 51 105 105 144 659	Weight 5.1% 1.8% 14.4% 0.6% 9.4% 50.3% 100.0%	Odds ratio M–H, Fixed, 95% C 0.08 [0.00, 1.42 0.57 [0.26, 1.27 1.10 [0.50, 2.42 0.30 [0.09, 1.03 0.56 [0.22, 1.47 0.34 [0.21, 0.55 0.46 [0.34, 0.63	Fav 21 21 21 21 21 21 21 21 21 21	Odds ra M-H, Fixed, S	Favors [control] C
Study or subgroup Donk (2017) lanssen (2015) .avelle (2018) MacDowall (2019) tadoliff (2017a) tadoliff (2017b) /accor (2018) Fotal (95% CI)	CDA Events 0 1 12 21 4 4 10 40	Total 50 103 124 67 164 225 263 969	ACD Events 5 2 160 150 8 8 54 108	F Total 47 106 101 51 105 105 144 659	Weight 5.1% 1.8% 14.4% 10.6% 8.6% 9.4% 50.3% 100.0%	Odds ratio M–H, Fixed, 95% C 0.08 [0.00, 1.42 0.51 [0.05, 5.71 1.10 [0.50, 2.42 0.30 [0.09, 1.03 0.56 [0.22, 1.47 0.34 [0.21, 0.55 0.46 [0.34, 0.63	Fav 2] ← 2] ← 2] 2] 2] 3] 3] 3] 3] 4]	Odds ra M-H, Fixed, S	Favors [control]
Study or subgroup Jonk (2017) lanssen (2015) .avelle (2018) Jacobild (2019) Jadoliff (2017a) Badoliff (2017b) /accaro (2018) Fotal (95% CI) Total (events) Pateronenisty: x ² = 8.47	CDA <u>Events</u> 0 1 12 21 4 10 40 88 off = 6 (P	Total 50 103 124 67 164 225 263 969 = 0.21)	ACD Events 5 2 160 150 8 8 54	F Total 47 106 101 51 105 105 144 659	Weight 5.1% 1.8% 14.4% 10.6% 8.6% 9.4% 50.3% 100.0%	Odds ratio M-H, Fixed, 95% C 0.08 [0.00, 1.42 0.51 [0.56, 5.71 1.05 [0.52, 1.27 1.10 [0.50, 2.42 0.30 [0.09, 1.03 0.56 [0.22, 1.47 0.34 [0.21, 0.55 0.46 [0.34, 0.63	Fav	Odds ra M–H, Fixed, 9	Favors [control]
Study or subgroup Donk (2017) anssen (2015) avelle (2018) MacDowall (2019) MacDiff (2017a) Madoliff (2017b) Vaccaro (2018) Total (95% CI) Total (events) Heterogeneity: $\chi^2 = 8.47$, Test for overall effects: 2	CDA Events 0 1 12 21 4 10 40 88 6 df = 6 (P = 2 2 - 4 79 (P = 2)	Total 50 103 124 67 164 225 263 969 = 0.21)	ACD <u>Events</u> 5 2 160 150 8 8 54 108 ; <i>f²</i> = 29% 001)	F Total 47 106 101 51 105 105 144 659	Weight 5.1% 1.8% 14.4% 10.6% 9.4% 50.3% 100.0%	Odds ratio M-H, Fixed, 95% C 0.08 [0.00, 1.42 0.51 [0.05, 5.71 0.57 [0.26, 1.27 1.10 [0.50, 2.42 0.30 [0.09, 1.03 0.56 [0.22, 1.47 0.34 [0.21, 0.55 0.46 [0.34, 0.63	Fav	Odds ra M-H, Fixed, 9	Favors [control]
Study or subgroup Donk (2017) Ianssen (2015) .avelle (2018) JacDowali (2019) Jadcliff (2017a) Jadcliff (2017b) Jaccaro (2018) Fotal (95% CI) Fotal (95% CI) Fotal (events) Heterogeneity: $\chi^2 = 8.47$, Fest for overall effects: Z	CDA <u>Events</u> 0 1 12 21 4 10 40 40 88 df = 6 (P : = 4.79 (P	Total 50 103 124 67 164 225 263 969 = 0.21) < 0.00	ACD <u>Events</u> 5 2 160 150 8 8 54 108 ; <i>I</i> ² = 29% 001)	F Total 47 106 101 51 105 105 144 659	Weight 5.1% 1.8% 14.4% 10.6% 8.6% 9.4% 50.3% 100.0%	Odds ratio M-H, Fixed, 95% C 0.08 0.00, 1.42 0.51 [0.05, 5.71 0.57 [0.26, 1.27 1.10 [0.50, 2.42 0.30 [0.09, 1.03 0.56 [0.22, 1.47 0.34 [0.21, 0.55 0.46 [0.34, 0.63	Fav	Odds ra M-H, Fixed, 1 0.1 Favors [CDA]	Favors [control]
Study or subgroup Jonk (2017) anssen (2015) avelle (2018) AacDowall (2019) Badcliff (2017a) Badcliff (2017b) faccaro (2018) Total (95% CI) Total (95% CI) Total (events) Heterogeneity: $\chi^2 = 8.47$. Test for overall effects: Z	CDA Events 0 1 12 21 4 10 40 88 df = 6 (P = 2 = 4.79 (P	Total 50 103 124 67 164 225 263 969 = 0.21) < 0.00	ACD <u>Events</u> 5 2 160 150 8 8 54 108 54 108 ; <i>I²</i> = 29% 001)	F Total 47 106 101 51 105 105 144 659	Weight 5.1% 14.4% 10.6% 8.6% 9.4% 50.3% 100.0%	Odds ratio M-H, Fixed, 95% C 0.08 0.08 0.00, 1.42 0.57 0.26, 1.27 1.10 0.50, 2.42 0.30 0.09, 1.03 0.56 0.22, 1.47 0.34 0.21, 0.55 0.46 [0.34, 0.63	Fav	Odds ra M-H, Fixed, 9 0.1 1 Favors [CDA]	Favors [control]
Study or subgroup Jonk (2017) anssen (2015) avelle (2018) AacDowall (2019) Aadcliff (2017a) Aadcliff (2017b) /accaro (2018) Total (95% CI) Total (events) leterogeneity: $\chi^2 = 8.47$, Test for overall effects: Z	CDA <u>Events</u> 0 1 221 4 10 40 40 88 6df = 6 (P = 2 = 4.79 (P	Total 50 103 124 67 164 225 263 969 = 0.21) < 0.00	ACD <u>Events</u> 5 2 160 150 8 8 54 108 ; <i>P</i> = 29% 001)	F Total 47 106 101 51 105 105 144 659	Weight 5.1% 1.8% 14.4% 10.6% 8.6% 9.4% 50.3% 100.0%	Odds ratio M–H, Fixed, 95% C 0.08 [0.00, 1.42 0.51 [0.05, 5.71 1.10 [0.50, 2.42 0.30 [0.09, 1.03 0.56 [0.22, 1.47 0.34 [0.21, 0.55 0.46 [0.34, 0.63	Fav	Odds ra M-H, Fixed, 9	Favors [control]
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Fig. 5 Forest plot showing a comparison of the frequency of adverse events (AE) between cervical disc arthroplasty (CDA) and anterior cervical discectomy and fusion (ACDF). (A) Total reported AE. (B) Serious AE. (C) Device/surgery-related AE. *Cl*, confidence interval.

Fig. 6 Forest plot comparing the incidence of adjacent segment degeneration (ASD) between cervical disc arthroplasty (CDA) and anterior cervical discectomy and fusion (ACDF). (A) Symptomatic ASD. (B) Radiological superior ASD. (C) Radiological inferior ASD. *Cl*, confidence interval.

LONG-TERM RESULTS COMPARING CDA AND ACDF

	C	DA	AC	DF		Odds ratio	Odds ratio
Study or subgroup	Events	Total	Events	Total	Weight	M–H, Random, 95% Cl	M–H, Random, 95% Cl
Burkus (2014)	19	276	39	265	17.6%	0.43 [0.24, 0.76]	
Coric (2018)	12	136	11	133	14.3%	1.07 [0.46, 2.52]	
Donk (2017)	1	50	6	47	5.0%	0.14 [0.02, 1.21]	
Hou (2017)	1	51	7	48	5.0%	0.12 [0.01, 0.99] -	
Janssen (2015)	7	103	19	106	13.6%	0.33 [0.13, 0.83]	
MacDowall (2019)	17	67	7	51	13.0%	0.14 [0.81, 5.63]	
Phillips (2015)	18	211	24	184	16.8%	0.62 [0.33, 1.19]	
Radcliff (2017b)	10	225	17	105	14.7%	0.24 [0.11, 0.55]	
Total (95% CI)		1119		939	100.0%	0.50 [0.29, 0.87]	•
Total events	85		130				
Heterogeneity: $\tau^2 = 0.35$	5, $\chi^2 = 19.2$	26, df =	7 (P = 0.0)	007); <i>l</i> ² :	= 64%		
Test for overall effects:	Z = 2.46 (/	P = 0.01)			0.01	0.1 1 10 100 Favors [CDA] Favors [ACDF]

	C	DA	AC	DF		Odds ratio	Odds	ratio	
Study or subgroup	Events	Total	Events	Total	Weight	M–H, Random, 95% Cl	M–H, Rand	om, 95% Cl	
Burkus (2014)	11	276	29	265	14.6%	0.34 [0.17, 0.69]			
Donk (2017)	0	50	5	47	2.4%	0.08 [0.00, 1.42]	· · ·	-	
Gornet (2019)	9	209	18	188	13.2%	0.42 [0.19, 0.97]			
Janssen (2015)	6	103	16	106	11.3%	0.35 [0.13, 0.93]			
MacDowall (2019)	15	67	3	51	8.3%	4.62 [1.26, 16.94]			
Phillips (2015)	17	211	24	184	15.5%	0.58 [0.30, 1.13]			
Radcliff (2017a)	5	164	5	81	8.5%	0.48 [0.13, 1.70]		_	
Radcliff (2017b)	10	225	11	105	12.4%	0.40 [0.16, 0.97]			
Vaccaro (2018)	10	236	22	144	13.8%	0.25 [0.11, 0.53]			
Total (95% CI)		1541		1171	100.0%	0.46 [0.29, 0.74]	•		
Total events	83		133						
Heterogeneity: $\tau^2 = 0.2$	7, χ ² = 17.6	8, df = 8	B(P = 0.02)	2); <i>I</i> ² = 5	55%			1	
Test for overall effects:	Z = 3.22 (I	P = 0.00	1)			C	0.0 0.1 1	10	100
							⊢avors [CDA]	Favors [ACDF]	



and patients' recommendation (OR = 3.23, 95% CI [1.79, 5.80], P < 0.00001; Fig. 8C).

Sensitivity Analysis

Combined OR or MD with 95% CI using fixed and random effects for all outcome measures are showed in Table 3. The consistency of the combined results was identified in overall success, NDI success, neurological success, radiological success, VAS neck pain and arm pain, SF-36 PCS and MCS, total reported AE, serious AE, device/surgery-related AE, symptomatic ASD, total secondary surgery, secondary surgery at the index level and at the adjacent level, and patients' satisfaction and recommendation rates. This means that these results are stable and reliable. However, the situation was quite different for NDI score, and radiological superior and inferior ASD, indicating that the combined results were unreliable. Therefore, further analysis was performed.

Then, we performed sensitivity analysis based on the leave-one-out method²⁷. For NDI score, we found that the combined result changed significantly when removing the study from Hou et al.³² or MacDowall et al.³⁵, with the Pvalue reduced from 0.06 to 0.02. Thus, we performed a subgroup analysis (Table 4) and found that the heterogeneity was 40% and 0% in the US and non-US subgroups, respectively, indicating that the heterogeneity originated from the studies from different regions. In addition, for radiological superior ASD, after we excluded the data from Radicliff et al. $(2017)^{37}$, I^2 decreased from 83% to 0%, and the statistical significance changed. For radiological inferior ASD, after we excluded the study from Phillips et al.³⁶, I^2 decreased from 78% to 28%, and the statistical significance also changed. This indicates that they were the source of heterogeneity for radiological superior and inferior ASD, respectively.

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Fig. 8 Forest plot comparing work status (A), patients' satisfaction (B), and patients' recommendation (C) between cervical disc arthroplasty (CDA) and anterior cervical discectomy and fusion (ACDF). *Cl*, confidence interval.

Subgroup Analysis

First, we performed subgroup analysis based on different regions. The included studies were classified into US and

non-US subgroups. The combined results of NDI score, symptomatic ASD, total secondary surgery, and secondary surgery at the index level and at the adjacent level are shown

	Fixed effects me	odel	Random effects model			
Outcome measures	Effect estimated	P-value	Effect estimated	P-value		
Overall success	2.10 [1.70, 2.59]	<0.00001	2.10 [1.70, 2.59]	<0.00001		
NDI success	1.73 [1.37, 2.18]	< 0.00001	1.73 [1.33, 2.26]	< 0.00001		
Neurological success	1.65 [1.24, 2.20]	0.0006	1.64 [1.19, 2.27]	0.003		
Radiological success	1.35 [0.88, 2.08]	0.17	1.36 [0.87, 2.10]	0.17		
NDI score	-2.67 [-4.33, -1.01]	0.002	-2.88 [-5.93, 0.17]	0.06		
VAS neck pain	-5.50 [-8.49, -2.52]	0.0003	-5.21 [-8.91, -1.51]	0.006		
VAS arm pain	-3.78 [-7.04, -0.53]	0.02	-3.77 [-7.08, -0.46]	0.03		
SF-36 PCS	1.93 [0.53, 3.32]	0.007	1.93 [0.53, 3.32]	0.007		
SF-36 MCS	2.62 [0.95, 4.29]	0.002	2.62 [0.95, 4.29]	0.002		
Total reported AE	1.14 [0.92, 1.42]	0.22	1.12 [0.80, 1.55]	0.51		
Serious AE	0.89 [0.71, 1.11]	0.29	0.88 [0.69, 1.13]	0.32		
Device/surgery-related AE	0.90 [0.68, 1.18]	0.43	0.89 [0.67, 1.18]	0.42		
Symptomatic ASD	0.46 [0.34, 0.63]	< 0.00001	0.49 [0.32, 0.76]	0.001		
Radiological superior ASD	0.69 [0.50, 0.95]	0.02	0.63 [0.28, 1.43]	0.27		
Radiological inferior ASD	0.53 [0.36, 0.78]	0.001	0.45 [0.19, 1.11]	0.08		
Total secondary surgery	0.52 [0.39, 0.69]	< 0.00001	0.50 [0.29, 0.87]	0.01		
Secondary surgery at the index level	0.46 [0.34, 0.61]	< 0.00001	0.46 [0.29, 0.74]	0.001		
Secondary surgery in the adjacent level	0.37 [0.28, 0.49]	< 0.00001	0.39 [0.28, 0.55]	< 0.00001		
Work status	1.28 [0.90, 1.82]	0.17	1.33 [0.78, 2.25]	0.29		
Patients' satisfaction rate	2.14 [1.50, 3.05]	<0.0001	2.14 [1.50, 3.06]	<0.0001		
Patients' recommendation rate	3.23 [1.79, 5.80]	< 0.0001	3.25 [1.81, 5.82]	< 0.0001		

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Outcome measurements		Included studies	Participants	I^2	Statistic effect model	Effect estimate	P-value
NDI score	US	6	1633	40%	MD (IV, Random, 95% CI)	-4.71 [-7.38, -2.04]	0.0005
	Non-US	2	252	0%	MD (IV, Fixed, 95% CI)	1.64 [-1.23, 4.51]	0.26
Symptomatic ASD	US	5	1413	0%	OR (M-H, Fixed, 95% CI)	0.40 [0.28, 0.58]	< 0.00001
	Non-US	2	215	68%	OR (M-H, Random, 95% CI)	0.42 [0.03, 5.57]	0.51
Total secondary surgery	US	5	1744	47%	OR (M-H, Fixed, 95% CI)	0.48 [0.35, 0.66]	< 0.00001
	Non-US	3	314	79%	OR (M-H, Random, 95% CI)	0.39 [0.04, 3.49]	=0.40
Secondary surgery at	US	7	2497	0%	OR (M-H, Fixed, 95% CI)	0.39 [0.29, 0.53]	< 0.0000
the index level	Non-US	2	215	85%	OR (M-H, Random, 95% CI)	0.73 [0.01, 46.24]	=0.88
Secondary surgery at	US	8	2722	27%	OR (M-H, Fixed, 95% CI)	0.35 [0.26, 0.47]	< 0.0000
the adjacent level	Non-US	2	215	0%	OR (M-H, Fixed, 95% CI)	0.77 [0.24, 2.51]	=0.67

in Table 4. Surprisingly, the combined results showed that CDA was superior to ACDF, with significant difference in all these outcome measures in the US subgroup. However, in the non-US subgroup, all these combined results were similar without statistical difference.

Second, we performed subgroup analysis based on the number of surgical levels. The combined results of overall success, neurological success, NDI success, radiological success, total reported AE, serious AE, device/surgery-related AE, secondary surgery at the index level and at the adjacent level, and patients' satisfaction rate are showed in Table 5. The combined results showed significantly less device/surgery-related AE of CDA in the two-level CDD group, with no statistical difference in single-level CDD. In contrast, patients' satisfaction favored CDA in single-level CDD (P = 0.0002), while in two-level CDD (P = 0.05), further studies are needed to identify the superiority. The residual outcome measures are similar for single-level and two-level CDD.

Assessment of Publication Bias

The funnel plot was applied to detect publication bias. As for neurological success (Fig. 9A), the funnel plots appeared symmetric and all studies were included inside, indicating that no publication bias existed. However, for secondary surgery at the adjacent level (Fig. 9B), the funnel plots appeared symmetric and 1 study was not included inside, indicating that publication bias existed.

TABLE 5 The combined results of subgroup analysis based on surgical level Included studies Participants ľ Statistic effect model Effect estimate P-value Outcome measurements Overall success Single-level 5 1218 0% OR (M-H, Fixed, 95% CI) 1.89 [1.47, 2.42] < 0.00001 Two-level 2 516 0% OR (M-H, Fixed, 95% Cl) 2.70 [1.83, 4.00] < 0.00001 NDI success Single-level 5 1382 27% OR (M-H, Fixed, 95% CI) 1.55 [1.17, 2.05] 0.002 Two-level 2 590 0% OR (M-H, Fixed, 95% Cl) 2.23 [1.46, 3.40] 0.0002 OR (M-H, Fixed, 95% CI) Neurological success Single-level 6 1449 9% 1.46 [1.04, 2.03] 0.03 Two-level 2 533 0% OR (M-H, Fixed, 95% CI) 2.44 [1.37, 4.34] 0.003 Radiological success Single-level 2 470 0% OR (M-H. Fixed, 95% C/) 1.68 [0.92, 3.05] 0.09 1.06 [0.56, 2.00] 2 532 OR (M-H, Fixed, 95% CI) Two-level 0% 0.87 Total reported AF 7 2145 40% OR (M-H. Fixed, 95% CI) 0.24 Single-level 1.14 [0.91. 1.43] Two-level 2 727 79% OR (M-H, Random, 95% CI) 1.34 [0.24, 7.49] 0.74 Serious AE Single-level 3 1029 43% OR (M-H, Fixed, 95% Cl) 0.95 [0.72, 1.26] 0.72 Two-level 2 727 0% OR (M-H, Fixed, 95% CI) 0.79 [0.54, 1.14] 0.20 5 Device/surgery-related AE Single-level 1590 0% OR (M-H, Fixed, 95% CI) 1.02 [0.75, 1.38] 0.91 Two-level 2 727 0% OR (M-H. Fixed, 95% CI) 0.51 [0.27. 0.96] 0.04 Secondary surgery at Single-level 6 1867 0% OR (M-H, Fixed, 95% CI) 0.37 [0.26, 0.52] < 0.00001 2 OR (M-H. Fixed, 95% CI) 0.004 the index level Two-level 727 0% 0.41 [0.22, 0.75] 7 2092 29% OR (M-H, Fixed, 95% Cl) <0.00001 Secondary surgery at Single-level 0.31 [0.22, 0.45] 2 727 the adjacent level Two-level 0% OR (M-H. Fixed, 95% Cl) 0.48 [0.28, 0.82] 0.007 Patients' satisfaction rate Single-level 3 705 0% OR (M-H, Fixed, 95% CI) 2.48 [1.55, 3.96] 0.0002 2 519 12% 0.05 Two-level OR (M-H. Fixed, 95% CI) 1.73 [1.00, 3.00]

AE, adverse event; CI, confidence interval; NDI, neck disability index; OR, odds ratio



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Fig. 9 The funnel plot of neurological success (A) and secondary surgery at the adjacent level (B). CI, confidence interval.

Discussion

Up to now, CDA application in spinal practice has remained controversial. Whether CDA is superior to ACDF has not been established in the long run ASD is always associated with the length of follow up. Therefore, it is crucial to evaluate the safety and efficiency of CDA in the long run. To our knowledge, there have been several metaanalyses comparing CDA with ACDF. Most of them have included partial long-term results, but they were mixed up with short-term and mid-term results^{5,16-23}. Therefore, given the availability of newly published long-term results²⁸⁻³⁸, we performed this study. This is the first time comparing the safety and efficiency of CDA with ACDF only focusing on long-term follow-ups.

In our meta-analysis, 11 RCT with more than 5 years' follow-up were identified. Based on the quality assessment criteria recommended by the Cochrane Back Review Group²⁵, all the studies were rated as low risk of bias. However, blinding to patients and care providers was not appropriately achieved in any studies. In addition, only 4 studies^{29,31,32,35} achieved blinding to outcome evaluators. This may result in reporting bias. Heterogeneity definitely existed in the included studies. First, various different types of CDA devices were used in the 11 RCT, including

Kineflex | C²⁹, Bryan^{30,34}, Discover³⁵ Secure-C³⁸, Prestige^{28,31}, Mobi-C^{32,37}, ProDisc-C³³, and PCM³⁶, differing in design and biomechanical properties. Second, the surgical level was different among studies. A total of 8 studies compared one-level CDD^{28-30,32-34,36,38}, 1 study compared two-level CDD³¹, and 2 studies compared both one-level and two-level $CDD^{35,37}$. Third, the region of studies was also different. Eight studies^{28,29,31,33,34,36–38} were conducted in the US and just 3 studies^{30,32,35} were out of the USA. Fourth, evaluation criteria of outcome measures varied among studies. Thus, we performed a sensitivity analysis including comparing two different effect models, using the leave-one-out method²⁷ and subgroup analysis to find the origin of heterogeneity. The combined results of radiological superior and inferior ASD were not stable and reliable and should be considered with caution. One possible reason is that only 2 studies reported this outcome^{36,37}. Although no publication bias existed in neurological success, publication bias existed in secondary surgery at the adjacent level.

After 5 years' follow up or more, our study revealed that CDA achieved a higher rate of clinical success and better functional outcome measurements with statistical significance, except for NDI score. A mid-term to longterm meta-analysis conducted by Hu et al.¹⁷ compared 4-7 years' clinical results, pooling data from 8 RCT, and showed that CDA achieved a significantly higher clinical success rate and better functional outcome. Similarly, Gao *et al.*⁵ compared 2–5 years' clinical results, pooling data for 14 RCT for analysis, and found that CDA was superior in VAS pain scores and neurological success, but NDI scores remained similar. In addition, major functional outcome measurements of CDA proved to have no obvious benefits when pooling 1-2 years' data into the analysis²⁴. This difference may originate from the different follow-up duration. Theoretically, CDA shares the same procedure of discectomy, endplate preparing, and decompression. VAS arm pain should be similar. However, VAS arm pain score was favored for CDA at the final follow up.

Adverse events are another major concern when applying CDA. Our results showed no statistical difference in total reported AE, serious AE, and device or surgery-related serious AE. This finding is consistent with some previous metaanalyses^{5,18,23} but contrary to others¹⁷. This difference can be explained by the different inclusion criteria for each study. Our study was focused on the long-term data and only enrolled RCT with more than 5 years' follow-up. Undeniably, pseudoarthrosis would not occur after CDA, but heterotopic ossification and bone loss became new problems^{12,14}. A recent systematic review¹⁴ showed that the long-term heterotopic ossification rate after CDA was 53.6% and the severe (grade 3 and 4) heterotopic ossification rate was 47.5%. In addition, the severe heterotopic ossification rate was significantly associated with follow-up time, with a 0.63% increase per month growth¹⁴. Bone loss was as high as 60.4%, although it did not affect mid-term to long-term clinical outcomes¹². This might be the reason why surgeons did LONG-TERM RESULTS COMPARING CDA AND ACDF

not feel confident recommending CDA as a standard option 30 . Moreover, it could explain the similar incidence of AE between CDA and ACDF.

Adjacent segment degeneration is the most important factor to be considered. The initial purpose of designing CDA was to prevent ASD after surgery. The biomechanical advantages have been well established^{3,49}. A recent metaanalysis showed that there was no statistically significant difference in ASD between CDA and ACDF within 24-months' follow-up period, but ASD was significantly lower with an increase of follow-up duration in CDA¹⁶. In contrast, Xu et al.²¹ and Zhu et al.²³ found that CDA was superior in reducing the ASD incident rate when compared with ACDF, and this superiority became more apparent over time²¹. Although these 3 studies^{16,21,23} attempted to evaluate ASD and symptomatic ASD separately, the follow-up period was not separated clearly, and long-term results were weak. Our results show that CDA has significantly lower symptomatic ASD. However, when we pooled all data together, there was no statistical difference in radiological superior ASD between CDA and ACDF. Interestingly, Ren et $al.^{20}$ found that ASD was not significantly different between CDA and ACDF with a smaller sample. Nunley et al.⁵⁰ (2018) summarized biomechanical and clinical evidence from worldwide application of CDA and concluded that CDA decreased the rate of radiographic adjacent segment pathology by alleviating adjacentlevel stress. However, the reason why subgroup analysis showed no significant difference in the non-US group is still difficult to explain.

Increased attention has been focused on the secondary surgery rate. Ghobrial et al.40 found that fewer patients with the Bryan disc required surgery for symptomatic ASD when compared with ACDF without statistical significance at 10 years' follow-up. However, they performed combined analysis using Bryan and Prestige artificial discs and found significant differences in symptomatic ASD requiring surgery as early as after 7 years⁴⁰. Surprisingly, MacDowall et al.⁵¹ conducted a retrospective study based on a Swedish database and found that CDA had a similar secondary surgery rate at the adjacent level but a higher secondary surgery rate at the index level with significant difference. However, based on our long-term results, CDA had a significantly lower rate of total secondary surgery, secondary surgery at the adjacent level, and secondary surgery at the index level, which is consistent with mid-term to long-term results¹⁷ However, this finding is contrary to the short-term to mid-term result reported by Zhang et al.⁵² that the secondary surgery rate at the adjacent level showed no significant difference. It seems that CDA exhibited superiority in reducing secondary surgery through restoring favorable physiological biomechanical properties in the long-term follow-up. However, it is important to note that our subgroup analysis also showed no statistical difference in the secondary surgery rate in the non-US group.

Several limitations may exist in this study. First, due to our focus on long-term results, only 11 RCT were included

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and 8 of them were conducted in the USA. Therefore, our study may not reflect the worldwide results and may result in bias. In addition, larger size samples are needed in future studies. Second, although all included studies were rated as low risk of bias based on the Cochrane Back Review Group, all of them failed to achieve sufficient blinding and the allocation concealment was rarely clearly described. Third, high heterogeneity exists in NDI score, radiological superior ASD and inferior ASD. Our sensitivity analysis results revealed that radiological superior ASD and inferior ASD were not stable and, therefore, should be considered with caution. Finally, subgroup analysis showed different results for NDI score, symptomatic ASD, total secondary surgery, secondary surgery at the index level, and secondary surgery at the adjacent level between US and non-US regions. Therefore, well-designed worldwide multi-center RCTs with long-term follow-ups are still needed for further evaluation in the future.

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Conclusion

Our study provided further evidence that CDA is superior in achieving long-term clinical outcomes such as overall success, NDI success and neurological success, VAS neck pain and arm pain, SF-36 PCS and MCS, symptomatic ASD, total secondary surgery, and secondary surgery at the index level and at the adjacent level. However, no clear benefit could be identified in regard to NDI score, total reported AE, serious AE, device/surgery-related AE, and radiological superior and inferior ASD. Well-designed worldwide RCT with long-term follow up are still necessary for further evaluation in the future.

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