



Cervical disc arthroplasty versus anterior cervical discectomy and fusion: a meta-analysis of rates of adjacent-level surgery to 7-year follow-up

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Background: Anterior cervical discectomy and fusion (ACDF) is an effective treatment for cervical spondylosis. A limitation of ACDF is the risk of adjacent-segment degeneration (ASD), owing to arthrodesis of a motion segment. Cervical disc arthroplasty (CDA) has hence garnered significant attention; yet, compelling evidence of reduction in ASD requiring surgery is lacking. This systematic review and meta-analysis sought to compare long-term longitudinal adjacent-level operation rates with CDA versus ACDF.

Methods: An electronic literature search was conducted. Eligible studies were multi-center randomized controlled trials (RCTs) comparing CDA with ACDF for one- or two-level symptomatic cervical spondylosis. The primary outcome was adjacent-level operation. Index-level reoperation was a secondary outcome. Outcomes were evaluated at 1-year intervals from the index operation to last reported follow-up by random-effects meta-analyses.

Results: Eleven RCTs met criteria. For one-level spondylosis, there was no difference in the rate of adjacent-level operation between CDA (2.3%) and ACDF (3.6%) at 2 years. However, a large difference favoring CDA became evident at 5 years and persisted at 7 years (4.3% *vs.* 10.8%, $P < 0.001$). Significantly fewer patients who underwent CDA required index-level reoperation at all time points out to 7 years (5.2% *vs.* 12.7%, $P < 0.001$). Similar to one-level operations, there was no significant difference in adjacent-level operations with two-level CDA (1.7%) versus two-level ACDF (3.4%) at 2 years. At 7 years, a significant difference favoring CDA became apparent (5.1% *vs.* 10.0%, $P = 0.014$). Two-level CDA resulted in fewer index-level reoperations out to 7 years (4.2% *vs.* 13.5%, $P < 0.001$).

Conclusions: In this meta-analysis, the short-term rate of adjacent-level operation was similar with CDA or ACDF. However, around 5 years, a statistically significant divergence emerged, where the rate of adjacent-level surgery rose steeply for ACDF. Index-level reoperations were less frequent with CDA in both the short- and long-term. These data indicate CDA may have a superior longevity to ACDF with regard to need for subsequent adjacent-level operation.

Keywords: Anterior cervical discectomy and fusion (ACDF); arthrodesis; arthroplasty; artificial disc; cervical disc arthroplasty (CDA); cervical spine; cervical spondylosis; disc prosthesis; disc replacement; fusion; myelopathy; radiculopathy

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Introduction

Anterior cervical discectomy and fusion (ACDF) is a safe and effective treatment for cervical spondylosis causing radiculopathy or myelopathy (1,2). However, the elimination of segmental motion with arthrodesis may increase the risk of adjacent-segment degeneration (ASD) (3,4). Cervical disc arthroplasty (CDA) has hence gained momentum over the last decade in effort to overcome this critical limitation of ACDF (5). CDA achieves the goals of decompression of the neural elements and maintenance of disc height and segmental lordosis, while also preserving physiologic segmental motion.

As a motion-sparing technology, CDA may mitigate the development of symptomatic ASD and need for subsequent reoperation. Nonetheless, clinical studies of CDA compared with ACDF have reported conflicting results regarding the effect on need for secondary adjacent-level surgery, which may be explained by a few reasons (6-8). First, these studies were not specifically powered to evaluate this outcome. Second, the development of symptomatic ASD is most relevant at long-term follow-up, whereas the primary endpoint of the majority of trials was at 2 years. To that end, leveraging statistical power by pooling data from randomized controlled trials (RCTs), we sought to perform a systematic review and meta-analysis of longitudinal reoperation rates out to long-term (≥ 4 -year) follow-up with CDA, as compared with ACDF, for symptomatic one- or two-level cervical spondylosis. Our hypothesis was that a divergence in rates of reoperation may begin to emerge at approximately 4 to 5 years, owing to increased rates of symptomatic ASD with ACDF over a longer time horizon.

Methods

This systematic review and meta-analysis of RCTs was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (9) and the Cochrane Handbook for Systematic Reviews of Interventions (10).

Search strategy

An electronic search of PubMed, EMBASE, and Web of Science was conducted on August 21, 2019 for randomized trials of CDA versus ACDF for cervical spondylosis. The search terms “anterior”, “arthrodesis”, “arthroplasty”, “artificial”, “cervical”, “disc”, “fusion”, “prosthesis”,

and “replacement” were used in relevant combinations (Supplementary). References of relevant resources and review articles were manually screened to supplement the search.

Eligibility criteria

Two authors (JH Badhiwala and CD Witiw) evaluated the search results for eligibility. Multi-center RCTs reporting adjacent- or index-level reoperations with CDA, as compared with ACDF, in adult patients with one- or two-level symptomatic (i.e., radiculopathy and/or myelopathy) cervical spondylosis were selected for inclusion. To be eligible, studies must have been published as English-language full-text reports in a peer-reviewed journal; conference abstracts were excluded. Detailed eligibility criteria are summarized in *Table 1*. *Figure 1* provides a flowchart of study eligibility.

Data extraction

Data were extracted from the trials' primary texts and supplementary appendices. For United States Food and Drug Administration (FDA) Investigational Device Exemption (IDE) trials, the corresponding FDA Summary of Safety and Effectiveness Data (SSED) documents were also evaluated for pertinent data. Data fields abstracted included: device name, authors, year of publication, number of centers, enrollment period, number of patients in each treatment arm, eligibility criteria, intervention, control, baseline patient characteristics, and outcomes. The primary outcome was adjacent-level reoperation. Index-level reoperation was evaluated as a secondary outcome. Outcomes were evaluated at 1-year intervals from the index operation to last reported follow-up.

Quality assessment

The methodological quality of included studies was evaluated using the Cochrane tool for assessing risk of bias in randomized trials, version 2 (RoB 2) (11). The RoB 2 provides an evaluation of the risk of bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Scores in these domains are distilled into a global assessment of the overall risk of bias in a given RCT: (I) ‘low risk of bias’; (II) ‘some concerns’; or (III) ‘high risk of bias’.

Table 1 Detailed inclusion and exclusion criteria

Eligibility	Population	Intervention	Control	Outcome	Study design
Inclusion	Adult patients (≥16 years)	CDA (any device)	ACDF	Index- or adjacent-level reoperations at fixed follow-up time periods (e.g., 2 years)	Multi-center
	One- or two-level cervical spondylosis		Allograft or cage	Minimum follow-up of 1 year	Randomized controlled trial
	Symptomatic with refractory radiculopathy or progressive myelopathy		Anterior plate	For mixed populations, outcomes reported separately for one- and two-level subgroups	English-language publication as a full-text report
Exclusion	Cervical spondylosis affecting more than two levels		Anterior cervical discectomy without fusion	Variable follow-up time periods (e.g., mean follow-up, 3 years; range, 1–5 years)	Single-center
	Cervical spondylosis at non-contiguous levels		Lack of anterior plate fixation (e.g., stand-alone cage)	Failure to distinguish between index- and adjacent-level reoperations	Non-randomized
			Autologous iliac crest bone graft	For mixed populations, lack of stratification of outcomes by one- or two-level cervical spondylosis	Use of historical controls
					Conference abstract
					Non-English language publication

CDA, cervical disc arthroplasty; ACDF, anterior cervical discectomy and fusion.

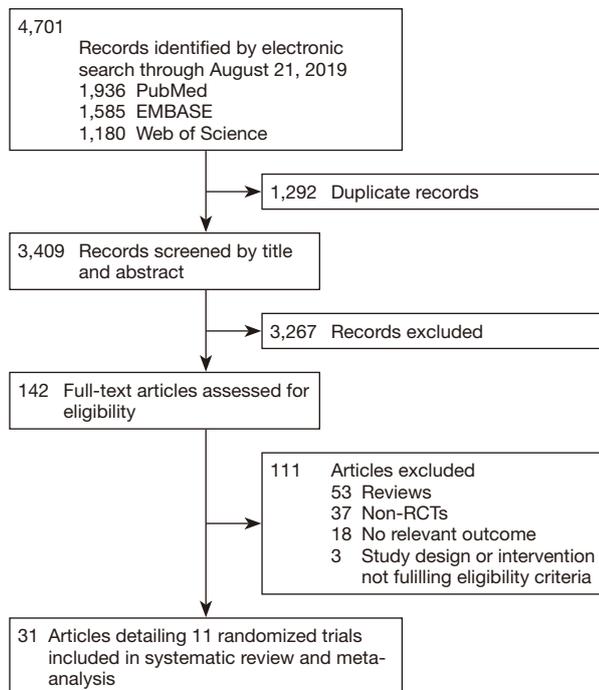


Figure 1 Flowchart of study eligibility.

Statistical analysis

For the purposes of reporting and analysis, multiple publications that reported the results of the same randomized trial at differing time points were grouped to permit longitudinal analysis of outcomes.

Descriptive statistics were by mean and standard deviation (SD) for continuous variables and count and percentage for categorical variables.

Outcomes were analyzed separately for one- and two-level operations; that is, randomized trials of CDA versus ACDF for one-level cervical spondylosis were pooled together in one analysis, whereas those for two-level cervical spondylosis were pooled together in a second separate analysis. Within each treatment arm, aggregate rates of adjacent- and index-level reoperation across trials at each follow-up time point were computed by random-effects meta-analyses based on the number of events and sample size of each trial. These were subsequently plotted over time for CDA and ACDF groups. For comparisons between CDA and ACDF, effect sizes for each trial were summarized

by odds ratios (ORs) and corresponding 95% confidence intervals (CIs), which were then pooled by random-effects meta-analyses. Meta-analyses were only performed when at least two studies reported outcomes for a given follow-up time point.

For all meta-analyses, outcomes were pooled by the DerSimonian and Laird method, with weights calculated by the inverse-variance method. Heterogeneity across trials was quantified by the I^2 , with I^2 values exceeding 25%, 50%, and 75% indicating a low, moderate, and high degree of heterogeneity, respectively.

Outcomes were analyzed by intention-to-treat, as reported by each trial (i.e., all randomized patients were included and analyzed according to the treatment group to which they were randomly assigned). All statistical analyses were performed using Comprehensive Meta Analysis version 3.3 (Biostat Inc) with a priori-specified significance level of $P=0.05$ (two-tailed).

Results

The search yielded 3,409 unique citations, of which 31 reports detailing 11 randomized trials for eight different devices—Bryan (Medtronic Sofamor Danek, Memphis, TN, USA); Kineflex|C (SpinalMotion Inc., Mountain View, CA, USA); Mobi-C (LDR Medical, Troyes, France); PCM (NuVasive Inc., San Diego, CA, USA); Prestige LP (Medtronic Sofamor Danek); Prestige ST (Medtronic Sofamor Danek); ProDisc-C (Synthes Spine, West Chester, PA, USA); and Secure-C (Globus Medical, Audubon, PA, USA)—met criteria (6-8,12-16) for inclusion (17-39). Of the 11 eligible studies, nine compared CDA with ACDF for one-level cervical spondylosis, whereas two examined two-level pathology. Of the nine one-level studies, seven were United States FDA IDE trials and two were multi-center RCTs from China. Both two-level studies were United States FDA IDE trials. A descriptive summary of eligible trials is provided in *Table 2*. Six trials had a ‘low risk of bias’ (12,17,22,27,30,33), five had ‘some concerns’ (7,15,21,25,38), and none were associated with a ‘high risk of bias’, as assessed by the Cochrane RoB 2 tool (*Table 3*). The primary source of potential bias in those trials deemed to have ‘some concerns’ generally related to lack of adequate description of the randomization process and allocation concealment. In one trial, there was additionally concern regarding deviation from the intended intervention, as 11 patients withdrew from the study because they desired the treatment to which they were not assigned (15).

Pooled rates of adjacent-level reoperation for one-level CDA compared with ACDF are summarized in *Figure 2*; a forest plot of effect sizes appears in *Figure 3*. There was no difference in the rate of adjacent-level reoperation between CDA (2.3%) and ACDF (3.6%) at 2 years (OR 0.67, 95% CI, 0.41–1.09, $P=0.106$). However, a very large difference favoring CDA became evident at 5 years. At 7-year follow-up, the rate of adjacent-level reoperation was only 4.3% in the CDA group versus 10.8% in the ACDF cohort (OR 0.37, 95% CI, 0.22–0.62, $P<0.001$). Rates of index-level reoperation are summarized in *Figure 4*; a forest plot appears in *Figure 5*. At 2 years, significantly fewer patients who underwent one-level CDA required index-level reoperation (3.2%), as compared with those treated with one-level ACDF (6.2%) (OR 0.51, 95% CI, 0.33–0.79, $P=0.002$). At 7 years, index-level reoperations occurred in only 5.2% of CDA patients, compared with 12.7% of the ACDF group (OR 0.39, 95% CI, 0.27–0.56, $P<0.001$).

With regard to two-level cervical spondylosis, rates of adjacent-level reoperation are provided in *Figure 6*; a forest plot appears in *Figure 7*. Similar to the one-level analysis, there was no significant difference in adjacent-level reoperations with two-level CDA (1.7%) versus two-level ACDF (3.4%) at 2 years. Nonetheless, at 7 years, a large and statistically significant difference favoring CDA became apparent (5.1% vs. 10.0%; OR 0.49, 95% CI, 0.27–0.87, $P=0.014$). Pooled rates of index-level reoperation are plotted in *Figure 8*; a forest plot of effect sizes is provided in *Figure 9*. Again, like the corresponding analysis of one-level studies, CDA resulted in fewer index-level reoperations at 2 years (2.8% vs. 9.3%; OR 0.26, 95% CI, 0.13–0.53, $P<0.001$) and also 7 years (4.2% vs. 13.5%; OR 0.27, 95% CI, 0.15–0.48, $P<0.001$).

Discussion

This paper calculates and provides longitudinal reoperation rates following CDA, as compared with ACDF, based on a rigorous systematic review and meta-analysis of published RCTs. For both one- and two-level symptomatic cervical spondylosis, this study found that in the short-term, up to 2 years, there was no statistically significant difference in adjacent-level reoperations with CDA versus ACDF. Nonetheless, rates of adjacent-level reoperation diverged over time, with reoperation rates with ACDF being significantly greater than CDA at long-term (≥ 4 -year) follow-up, likely owing to higher rates of symptomatic ASD. By contrast, index-level reoperations occurred

Table 2 Descriptive summary of eligible randomized trials of CDA versus ACDF for one- or two-level symptomatic cervical spondylosis

Author (year)	Trial	Enrollment	Population	Intervention	Control	Outcomes	Last follow-up	Sponsor/ funding
One-level								
Heller <i>et al.</i> [2009] (12); Sasso <i>et al.</i> [2011] (13); Ghobrial <i>et al.</i> [2019] (14); Lavelle <i>et al.</i> [2019] (8)	Bryan, US FDA IDE	May 2002–October 2004	N=463 30 centers One-level spondylosis Radiculopathy or myelopathy Refractory to 6 weeks of non-operative therapy, except myelopathy requiring immediate treatment Mean age: 44.4 yrs (CDA); 44.7 yrs (ACDF)	N=242 CDA (Bryan)	N=221 ACDF with allograft and anterior plate	NDI SF-36 Neck/arm pain VAS Neurological exam Work status Adverse events	10 years	Industry: Medtronic
Zhang <i>et al.</i> [2012] (15)	Bryan, China	May 2004–May 2006	N=109 3 centers One-level spondylosis, C3-7 Radiculopathy or myelopathy Refractory to 6 weeks of non-operative therapy Mean age: 44.8 yrs (CDA); 45.6 yrs (ACDF)	N=56 CDA (Bryan)	N=53 ACDF with allograft and anterior plate	Angular motion NDI Neck/arm pain VAS ROM Adverse events	2 years	Non-industry: Chinese Medical Doctor Association
Coric <i>et al.</i> [2011] (7); Coric <i>et al.</i> [2018] (16)	Kinflex C, US FDA IDE	July 2005–January 2010	N=269 21 centers One-level spondylosis Radiculopathy Mean age: 43.7 yrs (CDA); 43.9 yrs (ACDF)	N=136 CDA (Kinflex C)	N=133 ACDF with allograft and anterior plate	NDI Neck pain VAS Patient satisfaction Neurological exam Adverse events Radiographic ASD Angular motion Activity level	5 years	Industry: SpinalMotion

Table 2 (continued)

Table 2 (continued)

Author (year)	Trial	Enrollment	Population	Intervention	Control	Outcomes	Last follow-up	Sponsor/ funding
Hissey et al. [2014] (17); Hissey et al. [2015] (18); Hissey et al. [2016] (19); Jackson et al. [2016] (6); Radcliff et al. [2017] (20)	Mobi-C, US FDA IDE	April 2006– March 2008	N=245 23 centers One-level spondylosis, C3-7 Radiculopathy or myeloradiculopathy Refractory to non-operative therapy for 6 weeks or progressive symptoms Mean age: 43.3 yrs (CDA); 44.0 yrs (ACDF)	N=164 CDA (Mobi-C)	N=81 ACDF with allograft and anterior plate	NDI SF-12 Angular motion Neurological exam Adverse events	7 years	Industry: LDR Spine
Zhang et al. [2014] (21)	Mobi-C, China	February 2008– November 2009	N=111 11 centers One-level spondylosis, C3-7 Symptomatic Refractory to 3 months of non- operative therapy Mean age: 44.8 yrs (CDA); 46.7 yrs (ACDF)	N=55 CDA (Mobi-C)	N=56 ACDF with cage and anterior plate	JOA NDI Neck pain VAS ROM Adverse events	4 years	None
Phillips et al. [2013] (25); Phillips et al. [2015] (26)	PCM, US FDA IDE	January 2005- December 2007	N=403 One-level spondylosis, C3-4 to C7-T1 Radiculopathy or myelopathy Refractory to non-operative therapy May have undergone prior nonadjacent or adjacent single-level fusion	N=218 CDA (PCM)	N=185 ACDF with allograft and anterior plate	NDI SF-36 Neck/arm pain VAS Neurological status Adverse events Angular motion	7 years	Industry: NuVasive

Table 2 (continued)

Table 2 (continued)

Author (year)	Trial	Enrollment	Population	Intervention	Control	Outcomes	Last follow-up	Sponsor/funding
Murmaneni et al. [2007] (30); Burkus et al. [2010] (31); Burkus et al. [2014] (32)	Prestige ST, US FDA IDE	October 2002–August 2004	N=541 32 centers One-level spondylosis, C3-7 Radiculopathy or myelopathy Refractory to non-operative therapy (≥6 weeks) or progressive neurological worsening	N=276 CDA (Prestige ST)	N=265 ACDF with allograft and anterior plate	NDI Neck/arm pain VAS SF-36 Neurological exam Work status	7 years	Industry: Medtronic
Murray et al. [2009] (33); Delamarter et al. [2010] (34); Zigler et al. [2013] (36); Delamarter & Zigler [2013] (35); Janssen et al. [2015] (37)	ProDisc-C, US FDA IDE	August 2003–October 2004	N=209 13 centers One-level spondylosis, C3-7 Radiculopathy Refractory to non-operative therapy for at least 6 weeks Mean age: 42.1 yrs (CDA); 43.5 yrs (ACDF)	N=103 CDA (ProDisc-C)	N=106 ACDF with allograft and anterior plate	ROM Adverse events Secondary surgery NDI Neck/arm pain VAS Patient satisfaction Neurological exam SF-36 Adverse events	7 years	Industry: Synthes
Vaccaro et al. [2013]; Vaccaro et al. [2018] (38,39)	Secure-C, US FDA IDE	July 2005–April 2008	N=291 18 centers One-level spondylosis, C3-7 Radiculopathy or myelopathy Refractory to non-operative therapy (≥6 weeks) Mean age: 43.4 yrs (CDA); 44.4 yrs (ACDF)	N=151 CDA (Secure-C)	N=140 ACDF with allograft and anterior plate	Angular motion NDI Neck/arm pain VAS Neurological status SF-36 Range of motion	7 years	Industry: Globus Medical

Table 2 (continued)

Table 2 (continued)

Author (year)	Trial	Enrollment	Population	Intervention	Control	Outcomes	Last follow-up	Sponsor/funding
Two-level								
Davis et al. [2013] (22); Davis et al. [2015] (23); Jackson et al. [2016] (6); Radcliff et al. [2016] (24); Radcliff et al. [2017] (20)	Mobi-C, US FDA IDE	April 2006–March 2008	N=330 24 centers Cervical spondylosis at two contiguous levels, C3-7 Radiculopathy or myeloradiculopathy Refractory to 6 weeks of non-operative therapy Mean age: 45.3 yrs (CDA); 46.2 yrs (ACDF)	N=225 CDA (Mobi-C)	N=105 ACDF with allograft and anterior plate	NDI SF-12 Angular motion Neurological exam Adverse events	7 years	Industry: LDR Medical
Gornet et al. [2017] (27); Lanman et al. [2017] (28); Gornet et al. [2019] (29)	Prestige LP; US FDA IDE	June 2006–November 2007	N=397 30 centers Cervical spondylosis at two contiguous levels, C3-7 Refractory to 6 weeks of non-operative therapy Mean age: 47.1 yrs (CDA); 47.3 yrs (ACDF)	N=209 CDA (Prestige LP)	N=188 ACDF with allograft and anterior plate	NDI Neck/arm pain VAS SF-36 Gait abnormality ROM Neurological exam Adverse events	10 years	Industry: Medtronic

ACDF, anterior cervical discectomy and fusion; CDA, cervical disc arthroplasty; JOA, Japanese Orthopaedic Association score; NDI, Neck Disability Index; ROM, range of motion; SF-12, Short-Form 12; SF-36, Short-Form 36; VAS, visual analog scale.

Table 3 Assessment of the methodological quality (risk of bias) in included studies using the Cochrane RoB 2 tool

Trial	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall risk of bias
One-level						
Bryan, US FDA IDE	○	○	○	○	○	○
Bryan, China	□	□	○	○	○	□
Kineflex C, US FDA IDE	□	○	○	○	○	□
Mobi-C, US FDA IDE	○	○	○	○	○	○
Mobi-C, China	□	○	○	○	○	□
PCM, US FDA IDE	□	○	○	○	○	□
Prestige ST, US FDA IDE	○	○	○	○	○	○
ProDisc-C, US FDA IDE	○	○	○	○	○	○
Secure-C, US FDA IDE	□	○	○	○	○	□
Two-level						
Mobi-C, US FDA IDE	○	○	○	○	○	○
Prestige LP, US FDA IDE	○	○	○	○	○	○

○ , low risk of bias; □ , some concerns; △ , high risk of bias.

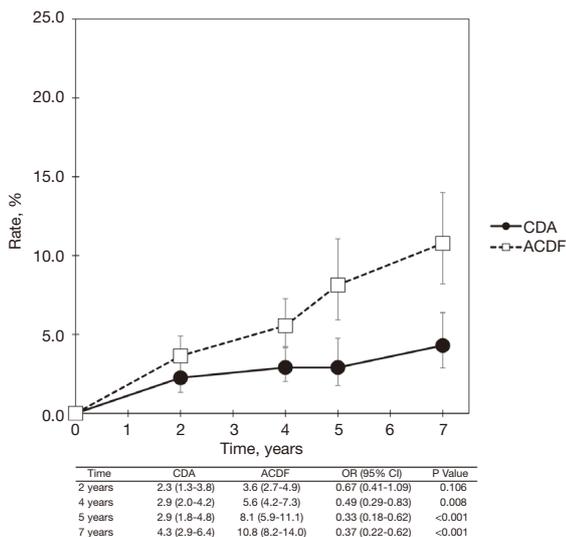


Figure 2 Pooled rates of adjacent-level reoperation for CDA compared with ACDF in patients with one-level symptomatic cervical spondylosis (derived from meta-analysis of nine randomized trials). CDA, cervical disc arthroplasty; ACDF, anterior cervical discectomy and fusion.

significantly less frequently with CDA at both short- and long-term follow-up. The findings of this study support a superior longevity with CDA versus ACDF with regard to need for reoperation.

It has been demonstrated that fusion alters spinal kinematics, such that motion, along with intradiscal pressures and shear strain, are increased at adjacent levels (3,4,40). These factors may predispose adjacent levels to accelerated degeneration, thus providing the rationale for CDA, which preserves physiologic segmental motion and may thereby mitigate ASD. The contemporary era of CDA devices began in 1989 with the design of a steel metal-on-metal artificial disc by Cummins, which was later redesigned and reintroduced as the Frenchay disc, and eventually purchased by Medtronic and marketed as the Prestige disc (41,42). Around the same time, American neurosurgeon, Vincent Bryan, designed the Bryan cervical disc (43). Since then, a number of additional devices have been developed and the evidence base has rapidly expanded. The current literature supports equivalent or superior outcomes with CDA compared with ACDF depending on the specific

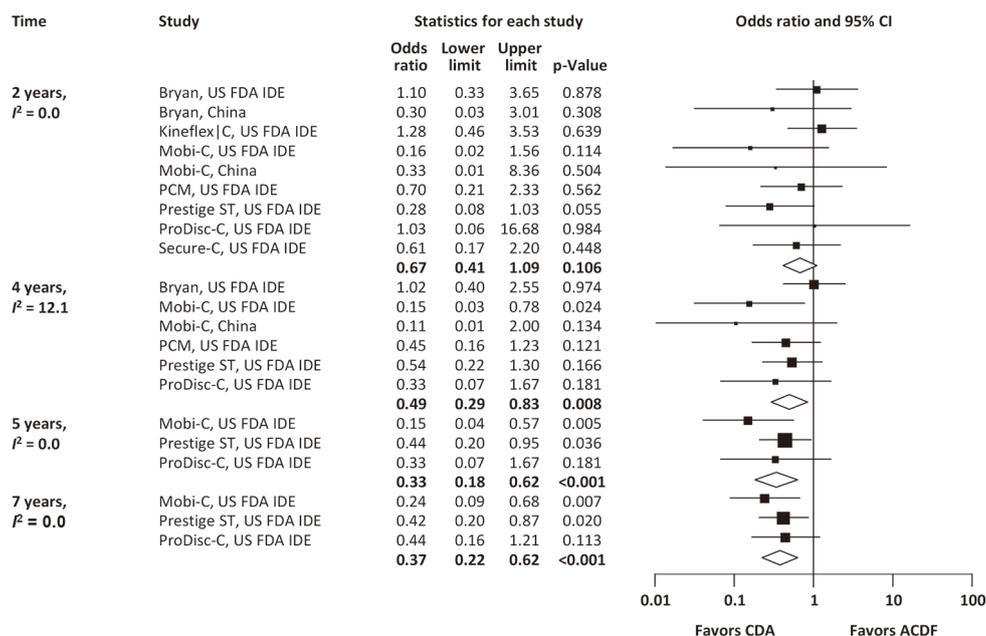


Figure 3 Forest plot of adjacent-level reoperations for CDA compared with ACDF in patients with one-level symptomatic cervical spondylosis (derived from meta-analysis of nine randomized trials). CDA, cervical disc arthroplasty; ACDF, anterior cervical discectomy and fusion.

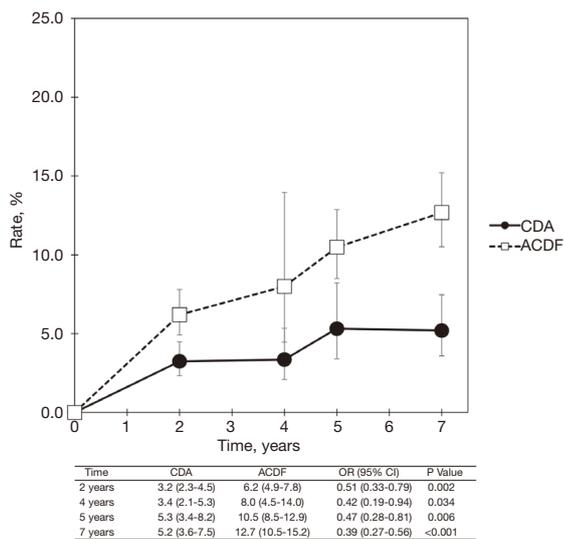


Figure 4 Pooled rates of index-level reoperation for CDA compared with ACDF in patients with one-level symptomatic cervical spondylosis (derived from meta-analysis of nine randomized trials). CDA, cervical disc arthroplasty; ACDF, anterior cervical discectomy and fusion.

outcome examined (44,45). Despite this, compelling evidence of benefit with regard to reduction in ASD requiring further surgery is lacking. One issue to consider is that individual trials in isolation are likely underpowered to detect a difference in adjacent-level reoperations. The primary outcome in United States FDA IDE trials of CDA, which sample size calculations are based on, is ‘overall success’, which is a composite outcome defined by: Neck Disability Index (NDI) score improvement ≥ 15 points; maintenance or improvement in neurological status; no additional surgical procedure classified as a ‘failure’; and no serious adverse event classified as implant-associated (30,46). Further, the primary outcome is evaluated at 2 years, when the cumulative rate of ASD is expectedly relatively low, making sample size requirements even greater. Long-term data with follow-up durations over 5 years have emerged only recently. These issues provided the impetus for the current meta-analysis examining longitudinal reoperation rates from RCTs of CDA versus ACDF.

There are multiple definitions of ASD (47,48). Imaging evidence of degenerative changes at adjacent levels (i.e.,

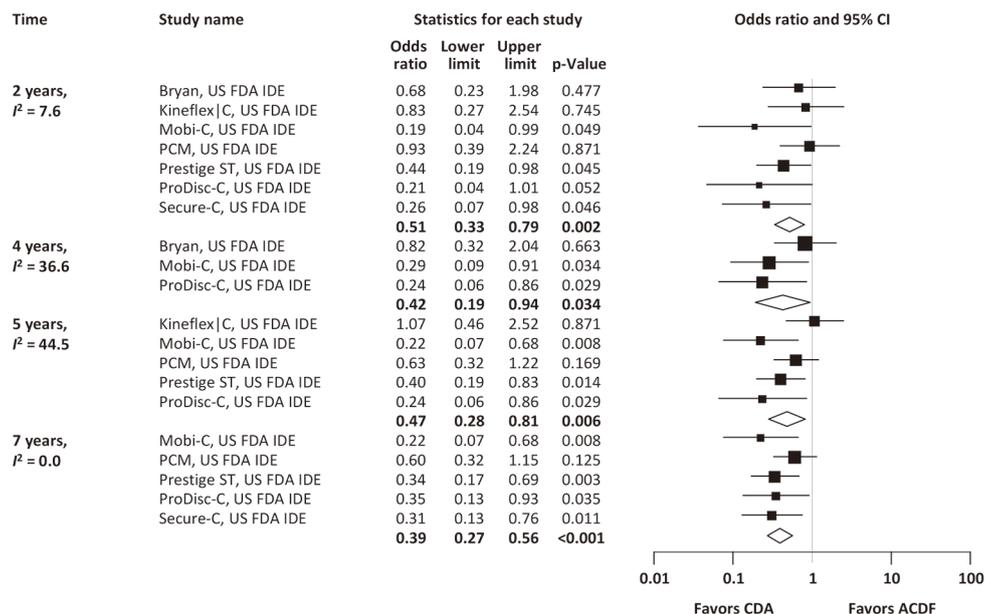


Figure 5 Pooled rates of index-level reoperation for CDA compared with ACDF in patients with one-level symptomatic cervical spondylosis (derived from meta-analysis of nine randomized trials). CDA, cervical disc arthroplasty; ACDF, anterior cervical discectomy and fusion.

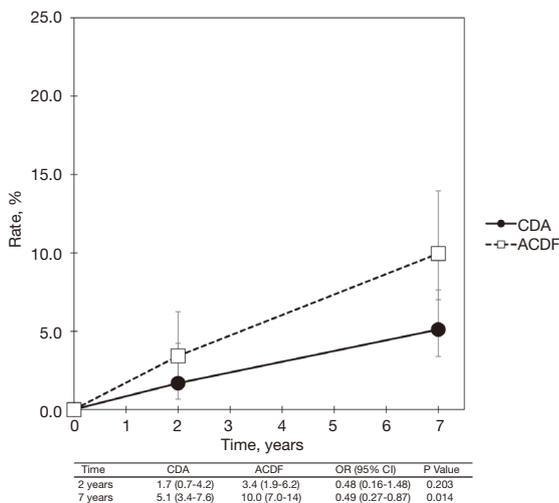


Figure 6 Pooled rates of index-level reoperation for CDA compared with ACDF in patients with one-level symptomatic cervical spondylosis (derived from meta-analysis of nine randomized trials). CDA, cervical disc arthroplasty; ACDF, anterior cervical discectomy and fusion.

radiographic ASD) after ACDF has been reported in up to 92% of patients at long-term follow-up (49). A subset of these patients will develop symptoms, radiculopathy and/or myelopathy, referable to the adjacent level (i.e., clinical ASD); a subset of these latter patients, still, will require secondary surgery to address the adjacent-segment pathology (50). Hilibrand *et al.* (4) retrospectively studied the incidence of symptomatic ASD following ACDF in 374 patients with up to 21-year follow-up. This study found that 25.6% of patients who had an anterior cervical fusion would develop clinical ASD at 10 years. Lee *et al.* (51) retrospectively studied 1,038 patients who underwent anterior cervical fusion; Kaplan-Meier analysis predicted that 22.2% of patients would require reoperation at adjacent segments by 10 years. While smoking, female sex, number of levels fused, and the specific levels fused have been identified as risk factors (4,51), the most important and obvious risk factor for development of symptomatic ASD, requiring surgery or not, is time. Hilibrand *et al.* (4) found symptomatic ASD developed at a relatively constant

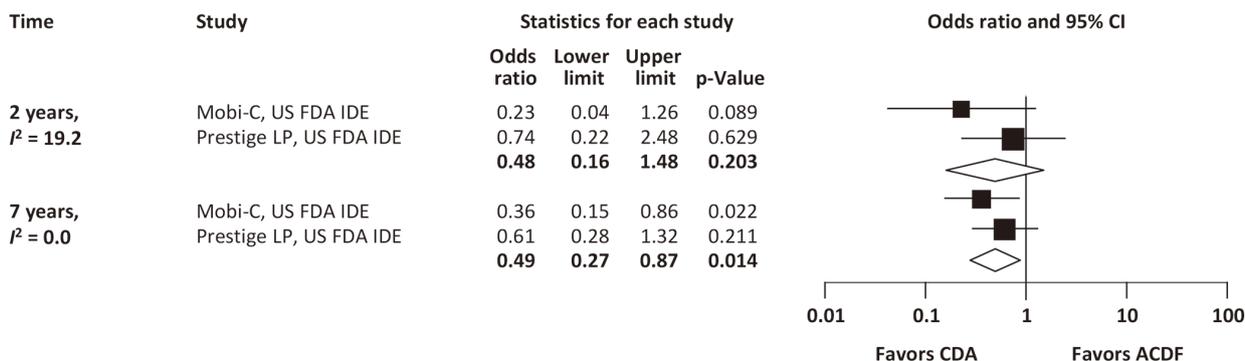


Figure 7 Forest plot of adjacent-level reoperations for CDA compared with ACDF in patients with two-level symptomatic cervical spondylosis (derived from meta-analysis of two randomized trials). CDA, cervical disc arthroplasty; ACDF, anterior cervical discectomy and fusion.

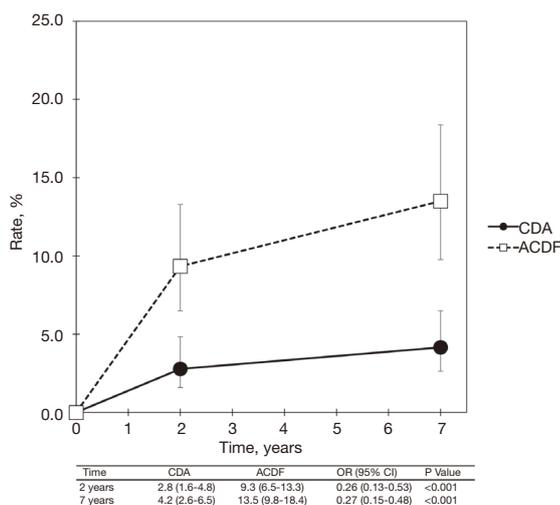


Figure 8 Pooled rates of index-level reoperation for CDA compared with ACDF in patients with two-level symptomatic cervical spondylosis (derived from meta-analysis of two randomized trials). CDA, cervical disc arthroplasty; ACDF, anterior cervical discectomy and fusion.

rate of 2.9% per year. Similarly, Lee *et al.* (51) noted that symptomatic ASD requiring operation occurred at a relatively consistent rate of 2.4% per year. Therefore, if CDA reduced the rate of development of symptomatic ASD, it would take several years to become apparent. In a consecutive cohort of 888 patients, Xu *et al.* (52) found ASD warranting secondary operation occurred at a mean of 47 months after the index ACDF in 108 patients (12.2%). Other series have reported an even longer time lag. Wang *et al.* (53) reported the average time to onset of ASD

requiring subsequent surgery to be 8.5 years. In the current meta-analysis, the rate of adjacent-level reoperation following single-level ACDF at 7 years was 10.8%; this represents an average rate of 1.5% per year. At 2 years, none of the one-level randomized trials included in this meta-analysis noted a significant difference in adjacent-level reoperations. By 4 years, a significant reduction with CDA occurred in the Mobi-C trial (US FDA IDE) and non-significant trends were noted for Mobi-C (China), PCM, Prestige ST, and ProDisc-C, such that the pooled treatment effect was statistically significant in favor of CDA. At 5 years, both the Mobi-C (US FDA IDE) and Prestige ST trials found a significant effect on adjacent-level reoperations, whereas a trend was observed for ProDisc-C; the pooled treatment effect of CDA in reducing adjacent-level reoperations was statistically significant and the magnitude of the effect was quite large. These findings persisted at the 7-year mark. Neither two-level study found a significant difference in adjacent-level reoperations at 2 years, but a significantly lower rate was seen for CDA in the Mobi-C trial at 7 years; the pooled treatment effect at 7 years was statistically significant in favor of CDA.

With regard to index-level reoperations, for both one- and two-level symptomatic cervical spondylosis, we observed a statistically significant lower rate for CDA compared with ACDF at all follow-up time points that could be examined, from 2 to 7 years. The majority of index-level reoperations in the ACDF group were likely due to persistent radiculopathy or symptomatic pseudarthrosis. Indeed, in an in-depth examination of subsequent surgery rates after CDA with the Mobi-C disc, Jackson *et al.* (6) reported that the most common reasons for reoperations

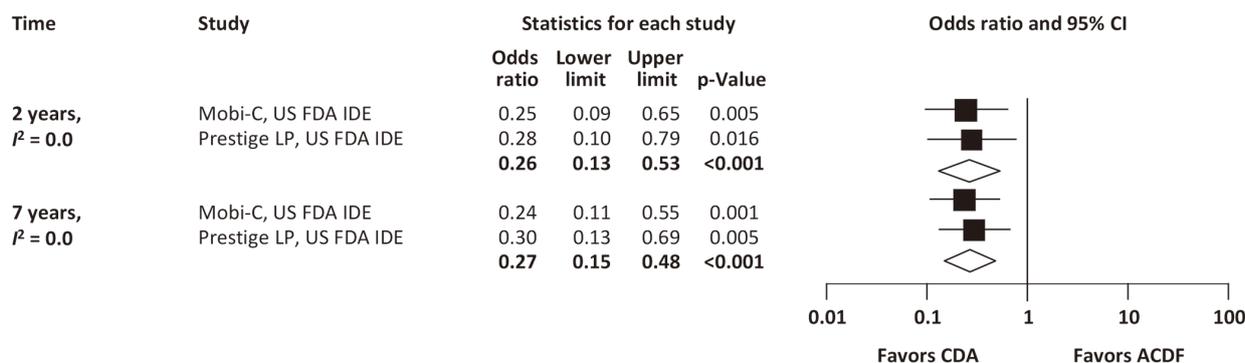


Figure 9 Forest plot of index-level reoperations for CDA compared with ACDF in patients with two-level symptomatic cervical spondylosis (derived from meta-analysis of two randomized trials). CDA, cervical disc arthroplasty; ACDF, anterior cervical discectomy and fusion.

at the index level for one- and two-level ACDF were radiculopathy, neck pain, and pseudarthrosis; by contrast, radiculopathy was the most common indication for secondary surgery among patients who underwent CDA.

The key strengths of this study include the greater statistical power derived from performing meta-analyses that pool data multiple trials; the longitudinal evaluation of reoperation rates out to 7-year follow-up; and the application of rigorous and uniform eligibility criteria to select only high-quality RCTs for analysis. Nonetheless, this study does have notable limitations. Any meta-analysis is limited to some degree by heterogeneity. Although all included studies used relatively similar patient selection criteria and outcome definitions, there remain important sources of heterogeneity. The most obvious and important source of heterogeneity would be that the artificial disc tested in each trial was a different device, with inherently different biomechanical properties and potential for efficacy. Despite this, we observed only low-to-moderate heterogeneity in meta-analyses of outcomes. Second, it should be recognized that the results of this systematic review and meta-analysis are inherently generalizable only to patients fulfilling the relatively specific indications and eligibility criteria used in the included studies.

Conclusions

This systematic review and meta-analysis of RCTs comparing CDA with ACDF for one- or two-level symptomatic cervical spondylosis found similar rates of adjacent-level reoperation with either intervention at 2 years. However, at 4 to 5 years, there developed a clear and statistically significant divergence, with the rate of adjacent-

level reoperation rising steeply for ACDF. By contrast, CDA was associated with a statistically significant lower rate of index-level reoperation at all follow-up time points examined. These findings support the superior longevity of CDA, as compared with ACDF, with regard to need for subsequent surgical intervention.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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