Cervical arthroplasty: what does the labeling say?

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OBJECTIVE The aim of this paper was to comprehensively review each of the Food and Drug Administration (FDA)–approved labels of 7 total cervical disc replacements, assess the exact methodology in which the trial was conducted, and provide a broad comparison of these devices to allow each surgeon to determine which disc best suits his or her specific treatment goals based on the specific labels and not the studies published.

METHODS The FDA-approved labels for each of the 7 artificial discs were obtained from the official FDA website. These labels were meticulously compared with regard to the statistical analysis performed, the safety and efficacy data, and the randomized controlled trial that each artificial disc was involved in to obtain the FDA approval for the product or device. Both single-level and 2-level approvals were examined, and primary and secondary end points were assessed.

RESULTS In the single-level group, 4 of the 7 artificial discs—Prestige LP, Prestige ST, Bryan, and Secure-C—showed superiority in overall success. Prestige ST showed superiority in 3 of 4 outcome measures (neurological success, revision surgery, and overall success), while the other aforementioned discs showed superiority in 2 or fewer measures (Prestige LP, neurological and overall success; Bryan, Neck Disability Index [NDI] and overall success; Secure-C, revision surgery and overall success; Pro-Disc C, revision surgery). The PCM and Mobi-C discs demonstrated noninferiority across all outcome measures. In the 2-level group, Prestige LP and Mobi-C demonstrated superiority in 3 outcome measures (NDI, secondary surgery, and overall success) but not neurological success.

CONCLUSIONS This paper provides a comprehensive analysis of 7 currently approved and distributed artificial discs in the United States. It compares specific outcome measures of these devices against those following the standard of care, which is anterior cervical discectomy and fusion. This information will provide surgeons the opportunity to easily answer patients' questions and remain knowledgeable when discussing devices with manufacturers.

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KEY WORDS anterior cervical discectomy and fusion; cervical arthroplasty; Food and Drug Administration

CERVICAL arthroplasty is one of the most carefully studied and documented spinal procedures. It has proven to be a safe and effective alternative to anterior cervical discectomy and fusion (ACDF) with allograft and instrumentation in selected patients with symptomatic cervical radiculopathy or myelopathy related to cervical degenerative disc disease.^{2,3,8,10,11,13,14,18–20} Cervical arthroplasty will preserve cervical spinal segmental motion following decompression of the neural elements. The procedure is associated with a positive neurological outcome. Over the last decade 7 arthroplasty devices have gained US Food and Drug Administration (FDA) approval:^{4,6,7,9,10,12,16} Bryan cervical disc (Medtronic Sofamor Danek USA

Inc.), Mobi-C cervical disc (LDR Spine USA Inc.), PCM cervical disc (NuVasive Inc.), Prestige LP and Prestige ST cervical discs (Medtronic Sofamor Danek), ProDisc-C total disc replacement device (Synthes Spine), and Secure-C cervical artificial disc (Globus Medical Inc.). While all of these devices have been approved for single-level arthroplasty, Prestige LP and Mobi-C have approval for use at 2 levels.

Data beyond the conventional 2-year time frame is regularly reported, and more recently the 7- and 10-year prospective outcomes of 2 randomized controlled trials comparing cervical arthroplasty with ACDF have been published.^{1,15} These comprehensive trials analyzed many

ABBREVIATIONS ACDF = anterior cervical discectomy and fusion; FDA = Food and Drug Administration; FSU = functional spinal unit; IDE = investigational device exemption; NDI = Neck Disability Index.

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outcome measures, but 4 were particularly important—the Neck Disability Index (NDI),¹⁷ neurological success, revision surgery, and overall success, with the latter being the primary end point.

Many positive and negative claims concerning these devices have been documented in the literature and presented from the podium. The statistical methods used in the published studies were not always identical to those used to obtain FDA approval. Information provided to surgeons from company representatives may not always be accurate. The FDA strictly regulates which claims can be validly presented for these devices based on its comprehensive review of each study design, the data generated, and the statistical method by which those data were assessed. This information is detailed in the product label, including preclinical testing results and precise details of the clinical study used to gain approval, such as adverse events, heterotopic calcification information, and so forth. Although many claims are made for each device, only a small number are approved by the FDA and appear in the label. The aim of this paper was to comprehensively review each of the FDA-approved labels for the 7 total cervical disc replacements, present the methodology and statistical data used to obtain FDA approval, and provide a comparison of these devices in terms of FDA-approved claims, which will allow each surgeon to determine which disc best suits his or her specific treatment goals.

Methods

This study is a review of the FDA-approved labels for each of 7 artificial discs.

The primary hypothesis of each clinical trial was a noninferiority hypothesis—that is, the overall success rate in the investigational group was statistically noninferior to the rate in the control group. As recommended by the FDA, a delta value ≥ 0.10 was used as the noninferiority margin. A patient's overall success was defined as the primary end point. The secondary hypothesis was a superiority hypothesis—that is, the success rate in the investigational group was statistically superior to the rate in control group.

All studies followed strictly established inclusion and exclusion criteria, which were almost identical across all 7 studies. Overall success required the inclusion of all of the following points. 1) The patient's NDI score improved by at least 20% or 15 points over baseline value. 2) The patient's neurological parameters (that is, sensorimotor function) and reflexes were maintained or improved. 3) No removals, revisions, reoperations, or additional fixations were required to modify any implant. 4) No adverse events related to treatment, the artificial disc or its implantation, or ACDF surgery or its associated implants or graft material occurred. The Prestige LP trial alone included the criterion of disc height success in its definition of overall success; that is, the functional spinal unit (FSU) anterior or posterior measurement height declined by no more than 2 mm compared with the 6-week postoperative assessment. These definitions were predefined in the protocol, based on the FDA's recommendation and guidance for investigational device exemption (IDE) clinical trials

for spinal devices. Neurological success was defined as the maintenance of or improvement in motor, sensory, and reflex function. All labels can be reviewed on the FDA's website (<http://www.fda.gov>).

Studies

Single-Level Arthroplasty

Bryan Cervical Disc. Patients were randomly assigned in a 1:1 ratio to 1 of 2 treatment groups: the Bryan cervical disc and ACDF. Bayesian statistical methods were planned to determine whether the investigational device was noninferior to the control with respect to the overall success rate at 24 months using a noninferiority margin of 10%. A total of 463 patients were treated at 30 investigational centers in the clinical trial: 242 patients in the investigational Bryan device treatment group and 221 patients in the control group. The results and conclusions in the FDA approval submission were based on an interim analysis of 300 patients with a 2-year follow-up as predefined in the protocol. The data used were obtained from 160 investigational patients and 140 control patients treated at 30 investigational centers.

Mobi-C Cervical Disc. The study was a prospective, multicenter, 2-arm, randomized (2:1), controlled noninferiority clinical study to compare the safety and effectiveness of the Mobi-C cervical disc prosthesis with those of ACDF. The study was designed using Frequentist statistical methods as a noninferiority trial with a margin (delta) of 10%. A closed testing procedure was used to allow superiority to be tested in the event that noninferiority was established for the primary effectiveness end point. Two hundred sixty subjects (179 Mobi-C and 81 ACDF) were enrolled in the study at 24 participating sites.

PCM Cervical Disc. This clinical study was based on the hypothesis that the primary overall success rate of the investigational PCM group was statistically noninferior to the ACDF control group's rate. A 1.3:1 (PCM disc/ACDF) randomization ratio was employed, and 494 patients were enrolled in the study at 23 clinical sites. Four hundred seventy-nine patients (289 PCM and 190 ACDF) were treated in the clinical trial. Data were assessed using Frequentist statistical methods.

Prestige ST Cervical Disc. This multicenter, prospective, randomized, noninferiority clinical trial compared the Prestige ST to ACDF in a 1:1 ratio (276 Prestige and 265 ACDF). Bayesian methods were used to assess the primary end point of noninferiority.

Prestige LP Cervical Disc. The study was a prospective, multicenter, nonrandomized, unmasked, noninferiority clinical trial comparing the Prestige LP cervical disc to a control cohort whose members underwent an ACDF in the Prestige ST trial. Two hundred eighty patients were treated with the investigational device at 20 centers, and 265 patients received the control treatment (ACDF) under the Prestige ST study. Bayesian methods were used to assess the primary end point of noninferiority.

ProDisc-C Total Disc Replacement Device. A noninferiority study design was employed. Using a fixed randomization blocking method of 4 assignments per block,

TABLE 1. Comparison of labeling characteristics of the 7 FDA-approved artificial discs for a single level

Disc (approval date)	Company	Study Design	Statistical Analysis	NDI	Neurological Success	Secondary Surgery	Overall Success
Prestige ST (2007)	Medtronic	RCT	Bayesian	Noninferior	Superior	Superior	Superior
ProDisc-C (2007)	Synthes	RCT	Frequentist	Noninferior	Noninferior	Superior	Noninferior
Bryan (2009)	Medtronic	RCT	Bayesian	Superior	Noninferior	Noninferior	Superior
Secure-C (2012)	Globus	RCT	Bayesian	Noninferior	Noninferior	Superior	Superior
PCM (2012)	NuVasive	RCT	Frequentist	Noninferior	Noninferior	Noninferior	Noninferior
Mobi-C (2013)	LDR	RCT	Frequentist	Noninferior	Noninferior	Noninferior	Noninferior
Prestige LP (2014)	Medtronic	Non-RCT (I = 280, C = 265)	Bayesian	Noninferior	Superior	Noninferior	Superior (w/o FSU)

C = control; I = intervention; RCT = randomized controlled trial.

a contract research organization generated random allocations in a 1:1 ratio. Ultimately, 209 patients (103 ProDisc-C and 106 ACDF) were enrolled at 13 investigational sites. Frequentist statistical methods were used to assess the primary end point of noninferiority.

Secure-C Cervical Artificial Disc. This study was a prospective, multicenter, 2-arm, randomized (1:1), unmasked, concurrently controlled, noninferiority clinical study to compare the safety and efficacy of the Secure-C cervical artificial disc to ACDF. Bayesian statistical methods were used to obtain the posterior probabilities of noninferiority and superiority, initially using a delta of 15%. Additional analyses using a delta of 10%, as requested by the FDA, were also incorporated. Three hundred eighty patients (236 Secure-C and 144 ACDF) were studied at 18 centers.

Two-Level Arthroplasty

Mobi-C Cervical Disc. The study was a prospective, randomized (2:1), multicenter, 2-arm, unmasked, concurrently controlled, noninferiority clinical study in subjects treated at 24 sites. A total of 339 subjects completed surgery, including 234 subjects treated with Mobi-C (225 randomized, 9 training) and 105 ACDF control subjects. FDA approval was obtained using data from 195 Mobi-C patients, 81 ACDF control patients, and 5 nonrandomized (training) Mobi-C patients. Frequentist statistical methods were used to test for noninferiority using an exact 95% 1-sided confidence bound for the difference between the study and control success rates; if a 10% offset could be ruled out according to the 95% lower bound, then superiority was to be tested. A closed testing procedure was used to allow superiority to be tested in the event that noninferiority was established for the primary effectiveness end point.

Prestige LP Cervical Disc. The study was a prospective, multicenter, randomized (1:1), unmasked, concurrently controlled, noninferiority clinical trial conducted

at 30 investigational sites. The study included a total of 397 subjects (209 Prestige LP and 188 ACDF). Bayesian methods were used to assess the primary end point of noninferiority.

Results

The details of each of the studies conducted and their results are presented in Tables 1 and 2. While most studies were prospective randomized controlled trials, the Prestige LP (2014) trial conducted by Gornet et al.⁴ was nonrandomized and compared the artificial disc group with a historical control group in which an ACDF had been performed. All reports were based on 2-year follow-up data. Noninferiority and superiority are not normally tested for second surgery rates as a prespecified noninferiority margin is not defined; however, secondary surgery is charted as superior or noninferior if there was a statistically significant difference between the 2 groups.

The single-level studies comprised patients with symptomatic single-level disease and no history of prior cervical spine surgery, except for the PCM study in which the symptomatic level could be adjacent to a previous fusion. All patients had to have neurological symptoms (radiculopathy and/or myelopathy) and failed nonoperative therapy. The cervical spinal alignment had to be normal, and instability could not be present. The control arm underwent instrumented allograft fusion. The full inclusion and exclusion criteria are listed in each label.

In the single-level group, 4 of the 7 artificial discs—Prestige LP, Prestige ST, Bryan, and Secure-C—showed superiority in overall success. Prestige ST showed superiority in 3 of the 4 outcome measures (neurological success, revision surgery, and overall success), whereas the other aforementioned discs showed superiority in 2 or fewer measures (Prestige LP, neurological and overall success; Bryan, NDI and overall success; Secure-C, revision surgery and overall success; Pro-Disc C, revision surgery). The PCM and Mobi-C discs demonstrated noninferiority

TABLE 2. Comparison of labeling characteristics of the 2 FDA-approved artificial discs for 2 levels

Disc (approval date)	Company	Study Design	Statistical Analysis	NDI	Neurological Success	Secondary Surgery	Overall Success
Prestige LP (2014)	Medtronic	RCT	Bayesian	Superior	Noninferior	Superior	Superior
Mobi-C (2013)	LDR	RCT	Frequentist	Superior	Noninferior	Superior	Superior

across all outcome measures. The PCM disc used adjacent to a fusion was associated with noninferiority in all categories. The superiority in overall success of Prestige LP in the single-level study did not include the data from FSU height. It should be noted that FSU was only assessed in the Prestige LP study and not in the other single-level disc studies.

The major inclusion and exclusion criteria for the 2-level studies were similar to those in the single-level studies except that 2 adjacent levels were treated. Subjects had to have symptomatic 2-level disease with radiculopathy and/or myelopathy from C-3 through C-7 that had failed to respond favorably to nonoperative therapy. Alignment had to be normal, and there could be no instability. The control arm underwent instrumented allograft fusion. The full inclusion and exclusion criteria are listed in each label. In the 2-level group, Prestige LP demonstrated superiority in all categories except neurological success.⁵ The Mobi-C cervical disc showed superiority in overall success and NDI and noninferiority in neurological success. The authors chose to grade the revision surgery as superior for the 2-level Mobi-C study. The rates presented in the summary of safety and effectiveness data are 3.8% for the arthroplasty group and 14.3% for the ACDF group, although no p value is presented.

Discussion

The opportunity to preserve motion and provide pain relief is of great value for patients with symptomatic cervical disc disease. The FDA published approval labels for the 7 cervical arthroplasty devices after each device completed an IDE pivotal study with a 24-month follow-up. These labels were published to inform surgeons of the indications, results, adverse events, and complications tied to each of the cervical arthroplasty devices. The FDA utilizes very strict criteria to determine noninferiority and superiority, and a superior level of efficacy in any parameter is difficult to achieve. The presentation of the data and the statistical instruments used in the clinical publications of these IDE studies do not always match those used to obtain approval.

Our study provides a comprehensive compilation of specific characteristics of each of the 7 devices, allowing a surgeon to choose which product would best suit a specific patient. It is important to note that the FDA constantly updates these labels and the results provided here are from the initial approvals of these devices.

Surgeons can choose which cervical arthroplasty device they would like to use to treat appropriate patients. It is not known why the devices have different superiority ratings in the different categories. These discrepancies could be related to the mechanics of articulation, undetected nuances in the study population, or some other factor. If a certain outcome measure(s) is particularly valued by a surgeon, then a device that produces a superior result compared with ACDF for that parameter(s) may be the best fit for that surgeon. This raises an important question—which device is going to be best for my patient?

Each of these studies was industry sponsored, which always raises concerns of bias. However, it should be re-

membered that the data collected in each of the studies were all heavily audited, which should work to mitigate this potential issue. The purpose of this paper was to establish a comprehensive list of each of the cervical device's FDA labels to provide surgeons with the data in a clear and concise reference document. This will provide surgeons the opportunity to easily answer patients' questions and remain knowledgeable when discussing devices with manufacturers.

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Author Contributions

Conception and design: Traynelis. Acquisition of data: Turel, Traynelis. Analysis and interpretation of data: all authors. Drafting the article: Turel, Kerolus. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Turel.

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