

Artificial Intervertebral Disc Arthroplasty for Treatment of Degenerative Disc Disease of the Cervical Spine



Assessment
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Executive Summary

Background

Approximately 60% of individuals aged 40 years and older have radiographic evidence of cervical degenerative disc disease (DDD) secondary to spondylosis. Symptoms can include neck and arm pain associated with radiculopathy or myelopathy. Untreated, the signs and symptoms of cervical DDD may diminish, stabilize, or worsen. Initial conservative therapies aim to relieve pain and prevent neurological injury. Typically, if at least 2 to 6 months of conservative treatment is ineffective, or the patient experiences progressive neurological or functional impairments, surgical intervention may be indicated.

Anterior cervical discectomy and fusion (ACDF) using autologous or allogeneic bone has long been considered the definitive surgical treatment for symptomatic DDD of the cervical spine. Recently, artificial intervertebral disc arthroplasty (AIDA) has been proposed as an alternative. AIDA uses virtually the same surgical approach as ACDF, but differs in that an artificial disc device is secured in the intervertebral space, rather than bone. It has been suggested that properly performed AIDA maintains anatomical disc space height, normal segmental lordosis, and physiological motion patterns at the index and adjacent cervical levels. Maintenance of physiological spinal motion patterns might then reduce risk for developing adjacent-level DDD felt secondary to altered mechanics at segments above or below the fusion site. This is the primary rationale for the development and use of artificial disc devices.

Objective

The objective of this Assessment is to determine whether AIDA improves health outcomes when used as an alternative to anterior-plated ACDF for patients with DDD of the cervical spine.

Search Strategy

MEDLINE[®] was searched (via PubMed) using the terms “cervical disc” and “replacement” or “prosthesis” and also with the term “cervical arthroplasty.” The search was performed through January 2009, limited to English-language articles on human subjects.

Selection Criteria

The Assessment focuses on the randomized, investigational device exemption (IDE) clinical trials of the Prestige ST and ProDisc-C artificial discs (approved via premarketing application [PMA] approval by the U.S. Food and Drug Administration [FDA] in July and December 2007, respectively). Studies using any non-FDA-approved or precursor devices were excluded.



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Main Results

Randomized, controlled trials of Prestige ST and ProDisc-C were reviewed. The designs of the two trials were nearly identical, employing similar inclusion and exclusion criteria, 24-month duration and follow-up schedule, study endpoints, success criteria, and noninferiority approach and margin (10%).

Primary outcome measures included the Neck Disability Index (NDI) and neurological status. The NDI is a multidimensional instrument assessing the effects of pain and disability on a patient's ability to manage everyday life. The tool includes 10 questions addressing neck pain intensity, personal care, lifting, reading, headaches, concentration, work, driving, sleeping, and recreation. A total NDI score is obtained by summing and then expressed as a percentage from 0% to 100%, with a lower percentage indicating less pain and disability. NDI response was reflected by improvement ≥ 15 . The neurological status outcome was a composite measure of motor function, sensory function, and deep tendon reflexes. Neurological success was defined as postoperative maintenance or improvement compared to preoperative status. Details of examiner expertise, blinding, intra- and interobserver variability were not reported in either trial. The primary composite endpoint ("overall success") was defined as attainment of all of the following: success as defined for the two primary outcome variables, plus a requirement for no serious implant- or procedure-associated adverse event, and no additional surgical procedure classified as a failure.

The Prestige ST disc was evaluated in a randomized, controlled trial in which disc arthroplasty (n=276) was compared to anterior-plated ACDF using allograft bone (n=265) (85% of those randomized to ACDF and 88% to AIDA underwent surgery). Participants were unblinded. Trial quality was rated poor due to systematic differences between the randomized and treated groups and unclear blinding of neurological assessments.

Patients (mean age 42.1 and 43.5 years in AIDA and ACDF arms, 46% male) had neck and arm pain secondary to DDD at a single level between C3 and C7 with documented presence of a herniated disc or osteophyte formation. Prior to surgery, all had received conservative therapy.

AIDA with the Prestige disc was noninferior to ACDF as assessed by the NDI with improvements of ≥ 15 in 84% and 81% of AIDA and ACDF patients, respectively. Neurological status was maintained or improved more often following AIDA (93% versus 84%, $p < 0.001$). For the overall success endpoint, AIDA was judged superior to ACDF (79% versus 68%, $p = 0.004$)—attributable to the neurological status component endpoint.

Perioperative and surgical outcomes were similar between treatment arms. Radiographic fusion was demonstrable for 97.5% of ACDF patients at 24-month follow-up. Cervical neck angular motion was maintained at preoperative levels in arthroplasty patients and restricted, as expected, in ACDF patients. Surgery at adjacent levels was performed in 3 (1.1%) of the AIDA arm and in 9 (3.3%) undergoing ACDF ($p = 0.07$, χ^2 1 df).

The ProDisc-C trial differed from the Prestige ST trial by blinding participants to study arm until following surgery. The multicenter trial (13 sites and 13 surgeons) included 209 patients (ProDisc-C, n=105; ACDF, n=106). Mean patient age was 42.1 and 43.5 years in AIDA and ACDF arms, with 46% and 49% male, respectively. At 24 months, follow-up rates were 98% in the ProDisc-C and 95% in the ACDF arms, respectively. Trial quality was rated fair due to inability to determine appropriateness of analyses and apparently unblinded neurological assessments.

AIDA with the ProDisc-C disc was noninferior to ACDF as measured by the NDI—an improvement of ≥ 15 in 80% and 78% of AIDA and ACDF patients, respectively. Neurological status was maintained or improved similarly in both groups: AIDA (91%) and ACDF (88%). For the overall success endpoint, AIDA was judged noninferior to ACDF (72% versus 68%), but not superior.

Secondary surgical procedures were more frequent following ACDF (8.5% versus 1.9%, absolute difference 6.6%; 95% CI: 0.6–12.5%). One patient (0.9%) in the ACDF arm underwent adjacent level fusion and none undergoing AIDA. Other perioperative and surgical outcomes were similar between groups.

Author's Comments and Conclusions

After 2 years' follow-up, trials of the Prestige ST and ProDisc-C discs found noninferiority as measured by the NDI and overall success composite outcome. Although informative, the evidence is not sufficient to allow concluding whether AIDA with either device is as beneficial as ACDF because of uncertainty regarding longer-term outcomes. Experience with ACDF and its high success rate requires a convincing rationale and supporting evidence to utilize a different procedure—noninferiority alone is insufficient. Neither trial provides adequate direct evidence over a relevant follow-up period (suggested to be 5 to 7 years) on subsequent adjacent-level DDD in control and investigational group patients.

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether artificial intervertebral disc arthroplasty as a treatment for DDD of the cervical spine meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

1. The technology must have final approval from the appropriate governmental regulatory bodies.

The Prestige ST and ProDisc-C Cervical discs received U.S. Food and Drug Administration (FDA) marketing approval in July and December 2007, respectively. The discs are indicated in skeletally mature patients for C3-C7 disc reconstruction following single-level discectomy for intractable radiculopathy and/or myelopathy. The devices are implanted via an open anterior approach. Intractable radiculopathy and/or myelopathy should present with at least one of the following items producing symptomatic nerve root and/or spinal cord compression that is documented by patient history (e.g., pain [neck and/or arm pain], functional deficit, and/or neurological deficit), and radiographic studies (e.g., CT, MRI, X-rays, etc.): 1) herniated disc, and/or 2) osteophyte formation.

A third product (Bryan Cervical Disc) received an approvable decision by an FDA advisory panel July 17, 2007, but had not received final marketing approval at the time this Assessment was originally prepared. As this Assessment was in press, the Bryan disc received PMA approval from the FDA (May 12, 2009). The Bryan disc is intended for use in patients similar to those for whom the Prestige device is indicated. As this Assessment excluded studies using any non-FDA-approved or precursor devices, evidence on the Bryan disc was not included in the original body of the Assessment; data on this device are included in Appendix C of this Assessment. The addition of these data does not change the conclusions of this Assessment.

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

Evidence derives from two randomized controlled trials designed to test noninferiority—one of the Prestige ST and the other of the ProDisc-C. The Prestige ST trial compared AIDA (n=276) with anterior plated ACDF using allograft bone (n=265); the ProDisc-C trial compared AIDA (n=103) with ACDF (n=106). The evidence is insufficient to support conclusions concerning the comparative effect of AIDA on health outcomes.

First, the evidence does not permit conclusions on the long-term performance of AIDA and adverse events. Device performance, durability, and revisability are key considerations for the relatively young population enrolled in these trials. The available evidence also is insufficient to permit conclusions as to whether or not AIDA affects the postsurgical development of adjacent-level DDD. In contrast, conclusions on the relative safety of cervical disc arthroplasty appear sufficiently supported in the short term.

Second, trial results demonstrated noninferiority for AIDA versus ACDF for the primary and overall success composite outcome. In the Prestige ST trial, while superiority with respect to the neurological status was found, and thus for the composite including it, quantitative data on neurological status are not available and it is not known whether it was obtained by blinded examiners, precluding interpreting its clinical meaning and relevance. Further, the Prestige ST trial did not find better outcomes of AIDA in terms of the NDI, a clinically validated, multidimensional outcome measure of neck pain and disability caused by cervical DDD. Taken together, these uncertainties preclude determining the comparative effect of AIDA on health outcomes.

3. The technology must improve the net health outcome; and

4. The technology must be as beneficial as any established alternatives.

The evidence does not permit conclusions as to whether AIDA for the cervical spine improves net health outcomes or is as beneficial as established alternatives.

5. The improvement must be attainable outside the investigational settings.

Whether artificial disc arthroplasty for the cervical spine improves the net health outcome has not been established in the investigational setting.

Based on the above, artificial intervertebral disc arthroplasty for the treatment of patients with cervical degenerative disc disease does not meet the TEC criteria.

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Assessment Objective

The objective of this Assessment is to determine whether artificial intervertebral disc arthroplasty improves health outcomes when used as an alternative to anterior cervical discectomy and fusion for patients with degenerative disc disease of the cervical spine.

Background

Cervical Degenerative Disc Disease

Cervical degenerative disc disease (DDD) is a manifestation of spinal spondylosis that causes deterioration of the intervertebral discs of the cervical spine (Emery 2001). Intervertebral discs are soft, spongy pads of tissue located between individual vertebrae, and act to absorb shock and stress of motion. While the exact causes of DDD are unclear, it is associated with aging, during which discs begin to lose proteoglycans, particularly chondroitin sulfate, leading to moisture loss. Dessicated discs become inelastic, with development of small microfissures and herniation of the nucleus pulposus. This is followed by settling and collapse of the index level segment, which affects the structure of the spinal column, causes abnormal spinal motion patterns and eventually results in the formation of spurs where the annular fibers insert near the end plate, in the facet joints, and at the uncovertebral joints. Bone spurs may narrow the foramen and impinge on nerve roots, resulting in pain and, ultimately, disability. Symptoms of cervical DDD include arm pain, weakness, and paresthesias. Disc herniation, osteophytes, kyphosis or instability that compress the spinal cord result in myelopathy, which is manifested by subtle changes in gait or balance, weakness in the arms or legs and numbness of the arms or hands, in severe cases.

The prevalence of DDD secondary to cervical spondylosis increases with age. Approximately 60% of individuals older than 40 years have radiographic evidence of cervical DDD. By age 65, 95% of men and 70% of women have at least one degenerative change evident at radiographic examination. It is estimated that some 5 million adults in the U.S. are disabled to an extent by spine-related disorders, although only a small fraction of those are candidates for spinal surgery. Still, surgery for cervical DDD has increased substantially in recent years. Based on the Nationwide Inpatient Sample (NIS), a probability survey of discharges from

nonfederal hospitals within the U.S., cervical spinal fusion in the U.S. increased from 26 per 100,000 in 1993 to 50 per 100,000 in 2003 (Cowan et al. 2006).

Treatment of Cervical DDD

Conservative Therapy. If untreated, the signs and symptoms of cervical DDD may diminish, stabilize, or worsen (Emery 2001). Initial conservative, noninvasive therapies are directed at relieving pain and preventing permanent injury to the spinal cord and nerves. These include rest; application of ice or heat; anti-inflammatory or analgesic agents; exercise; physical therapy; or support appliances such as a cervical collar or pillow. Typically, if 6 months of conservative treatment is ineffective, or the patient becomes unable to perform activities of daily living due to progression of pain or neurological symptoms in a shorter time frame, surgical intervention is indicated. Additionally, both radiculopathy and myelopathy are manifestations of cervical DDD that warrant consideration for surgical intervention. Axial neck pain alone attributed to cervical spondylosis is typically treated conservatively. However, certain patients without radiculopathy or myelopathy but with significant, intractable neck pain have cervical stenosis that requires surgical intervention if conservative treatments fail.

Surgical Fusion. Numerous surgical methods, instrumentation, and bone graft sources for spinal fusion have been investigated over the past several decades. However, anterior cervical discectomy and fusion (ACDF) is currently considered definitive surgical treatment for symptomatic single-level DDD of the cervical spine (Irwin et al. 2005). The goals of ACDF are to relieve pressure on the spinal nerves (decompression) and to restore spinal column alignment and stability. Resolution of pain and neurological symptoms may be expected in more than 80% to 100% of ACDF patients (Xie and Hurlbert 2007; Yue et al. 2005). The current procedure involves an anterolateral surgical approach, decompression of the affected spinal level, discectomy, and emplacement of either autograft or allograft bone in the prepared intervertebral space to stimulate healing and eventual fusion between the vertebral endplates. A metal anterior cervical plate is attached to the adjoining vertebral bodies to stabilize the fusion site, maintain neck lordosis, and reduce the need for prolonged postoperative brace application that is needed following ACDF without an anterior plate.

The choice of bone material for interbody fusion in ACDF has important clinical implications. Allograft bone has several drawbacks, including a minute (albeit unproven) risk of infectious disease transmission; possible immunological reaction to the allograft; and, possible limited commercial availability of appropriate graft material (Malloy and Hilibrand 2002). In contrast, the use of autograft bone in ACDF has potentially substantial morbidities at the harvest site, generally the iliac crest (Galler and Sonntag 2003). These include moderate-to-severe, sometimes prolonged pain; deep infection; adjacent nerve and artery damage; and, increased risk of stress fracture. Although there may be slight differences between autograft and allograft sources in the postoperative rate of union, clinical studies demonstrate similar rates of postoperative fusion (90–100%) and satisfactory outcomes for single-level, anterior plated ACDF using either bone source (Fraser and Hartl 2007; Samartzis et al. 2005; Yue et al. 2005; Suchomel et al. 2004). Thus, the choice of graft material involves a trade-off between the risks specific to autograft harvest versus those specific to use of allograft material. This choice is usually left to the patient, based on thorough explanation of the relative risks and benefits by the surgeon.

Artificial Intervertebral Disc Arthroplasty.

Artificial intervertebral disc arthroplasty (AIDA) is proposed as an alternative to ACDF for patients with symptomatic cervical DDD (Anderson et al. 2007; Smucker and Sasso 2006; Phillips and Garfin 2005; Anderson and Rouleau 2004). Disc arthroplasty and ACDF for single-level disease have very similar surgical indications, primarily unremitting pain due to radiculopathy or myelopathy, weakness in the extremities, or paresthesia (Brown and Heller 2006; McAfee 2004). However, the chief complaint in AIDA candidates should be radicular or myelopathic symptoms in the absence of significant spondylosis. Patients with advanced spondylosis or hard disc herniations have a separate pathology and require a different surgical approach (Brown and Heller 2006).

In AIDA, an artificial disc device is secured in the prepared intervertebral space rather than bone. An anterior plate is not placed to stabilize the adjacent vertebrae and a postsurgical external orthosis is usually not required. The surgical procedure and perioperative complications of AIDA are nearly identical to those of anterior fusion (Goffin 2006). It is suggested that AIDA

maintains anatomical disc space height, normal segmental lordosis, and physiological motion patterns at the index and adjacent cervical levels (Sears et al. 2006). This has been proposed to reduce the risk of adjacent-level DDD above or below a fusion site, and has been the major rationale driving device development and use. However, while biomechanical modeling studies have suggested that altered adjacent segment mechanics following fusion may lead to adjacent-level DDD, the long-term clinical relevance of these changes has not been established (Anderson et al. 2007; Phillips and Garfin 2005; Wigfield et al. 2002).

Appendix Table A summarizes information on 4 artificial cervical discs in the approval pipeline, in various stages of development in the U.S. This Assessment found no direct comparative data on any of these discs to base selection of one over another.

Outcome Measures

Outcome measures assessed in AIDA trials include the Neck Disability Index (NDI), neurological status, and functional spinal unit height (FSU). The NDI is a multidimensional instrument assessing the effects of pain and disability on a patient's ability to manage everyday life (Vernon and Mior 1991). The tool includes 10 questions addressing neck pain intensity, personal care, lifting, reading, headaches, concentration, work, driving, sleeping, and recreation. The response to each question ranges from 1 to 5, with a lower numeric score representing a better pain and disability status for that variable. A total NDI score is obtained by summing and then expressed as a percentage from 0% to 100%, with a lower percentage indicating less pain and disability. While the NDI is generally considered a validated instrument, in a sample of 137 patients with mechanical neck pain, Cleland et al. (2008) found test-retest reliability fair to moderate. They suggested a minimal clinically important difference of 19 percentage points.

Neurological status was a composite measure of motor function, sensory function, and deep tendon reflexes. It is used to judge if patients are within normal parameters for those categories based on physiological measurement. Neurological success was based on postoperative maintenance or improvement compared to preoperative status for each component. Because of potential subjectivity, considerations important to assess validity of neurological

exam findings in a clinical trial include examiner expertise, blinding, intra- and inter-observer variability.

The anterior FSU height is a radiographic measure of interdiscal space. Comparison of the immediate postoperative FSU height with the 6-week postoperative value shows whether or not the disc space has decreased, which indicates graft or device subsidence has occurred. While included in the Prestige ST trial protocol and in FDA documents, due to measurement difficulties, FSU was not included in the final analysis.

Secondary outcome measures include the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) mental (MCS) and physical (PCS) component summaries, neck and arm pain status, patient satisfaction, patient global perceived effect, gait assessment, foraminal compression test, adjacent level stability and measurements, return to work, and physician's perception.

FDA Status. Two cervical disc arthroplasty products (Prestige ST Cervical Disc and ProDisc-C) have received FDA premarket application (PMA) approval as Class III devices. Both are indicated in skeletally mature patients for C5-C7 disc reconstruction following single-level discectomy. They are implanted using an open anterior approach. They are indicated when intractable radiculopathy and/or myelopathy presents with at least one of the following findings producing symptomatic nerve root and/or spinal cord compression that is documented by patient history (e.g., pain [neck and/or arm pain], functional deficit, and/or neurological deficit), and radiographic trials (e.g., CT, MRI, X-rays, etc.): 1) herniated disc, and/or 2) osteophyte formation. The FDA required postapproval trials for both discs to evaluate the long-term (7-year) safety and effectiveness of these discs.

A third disc (Bryan® Cervical Disc, Medtronic) was deemed “approvable” by an FDA advisory committee on July 17, 2007, for treatment using an anterior approach of single-level cervical DDD defined as any combination of the following: disc herniation with radiculopathy; spondylotic radiculopathy; disc herniation with myelopathy, or spondylotic myelopathy. As this Assessment was in press, the Bryan disc received PMA approval from the FDA (May 12, 2009). As this Assessment excluded studies

using any non-FDA-approved or precursor devices, evidence on the Bryan disc was not included in the original body of the Assessment; data on this device are included in Appendix C of this Assessment (Heller et al. 2009).

Several other devices are under study in FDA IDE trials in the U.S., but final approval of those is not expected for several years (see Appendix Table A1).

Methods

Search Strategy

MEDLINE® was searched (via PubMed) using the terms “cervical disc” and “replacement” or “prosthesis” and also with the term “cervical arthroplasty.” The search was performed with no time limitation through January 2009, limited to English-language articles on human subjects. Review articles and meta-analyses provided background information. The bibliographies of retrieved articles were consulted to identify references that may have been overlooked by the electronic search. The “related articles” function was used in conjunction with key articles to identify other papers that may have been missed by the search process. Manufacturers and other vendor websites were consulted for information on commercial products.

Study Selection

The Assessment focuses on the randomized, investigational device exemption (IDE) clinical trials of the Prestige ST and ProDisc-C artificial discs. Clinical results for the Bryan disc were originally not considered as the device had not received final FDA approval. As this Assessment was in press, the Bryan disc received PMA approval from the FDA (May 12, 2009). Data on this device are included in Appendix C of this Assessment. Data from the Bryan IDE PMA submission were compiled in a previous TEC Assessment (Vol. 22, No. 7). Studies were excluded if they either used a precursor device to the current approved iteration or presented preliminary or incomplete data.

Medical Advisory Panel Review

Current Assessment. This Assessment was reviewed by the Blue Cross and Blue Shield Association's Medical Advisory Panel (MAP) on February 18, 2009. To maintain the timeliness of the scientific information in this Assessment, literature search updates were performed subsequent to the Panel's review (see “Search

Methods”). If the search updates identified any additional studies that met the criteria for detailed review, the results of these studies were included in the text where appropriate. There were no studies that would alter the conclusions of the Assessment.

Previous Assessment. A previous Assessment of AIDA was reviewed by the MAP in October 2007. At that time, it was decided that the available evidence was insufficient to permit conclusions regarding the use of AIDA in patients with cervical DDD who are surgical candidates because of chronic pain or neurological symptoms.

Formulation of the Assessment

Patient Indications

Surgical candidates have chronic pain or neurological symptoms secondary to cervical DDD at a single level between C3 and C7, lack of improvement with at least 6 weeks of nonoperative treatment, and no contraindications for the procedure. The indications and contraindications for cervical AIDA are fundamentally the same as those for ACDF, thus making artificial cervical disc arthroplasty an option in patients for whom ACDF is indicated.

Specific contraindications for AIDA include the presence of an active infection and stainless steel allergy. Other contraindications include cervical instability; more than one cervical level requiring surgical treatment; fused level adjacent to the treatment level; severe facet joint pathology; osteopenia, osteomalacia, osteoporosis, or spinal metastases.

Technologies to be Compared

AIDA is compared to single-level ACDF utilizing anterior plate fixation and an interbody allograft bone disc.

Health Outcomes

Benefits. Potential benefits of AIDA for treatment of cervical spine DDD include pain relief; decreased disability; amelioration of neurologic symptoms; maintenance of index level motion and function. The occurrence of adjacent-level DDD is hypothesized to be less common with AIDA.

Harms. Potential harms of AIDA include worsened pain and symptoms; perioperative complications; and, device- and procedure-

specific complications, for example, revision to ACDF.

Figure 1 graphically displays the relevant health states, transitions, and associated outcomes. As shown, comparing health outcomes of AIDA to ACDF requires that for each procedure, sufficiently certain evidence must be available to determine proportions experiencing each outcome or state encircled and transitions between them over the clinically relevant time horizon.

Specific Assessment Question

Does AIDA improve health outcomes as measured by pain relief, amelioration of neurologic symptoms, and restoration of function among patients with chronic pain and neurologic symptoms caused by radiculopathy or myelopathy secondary to single-level DDD of the cervical spine, as compared to ACDF utilizing anterior fixation and allograft bone interbody graft?

Review of Evidence

Prestige ST Disc IDE Clinical Trial

Methods. Information on the pivotal IDE trial submitted in support of the Medtronic PMA application for the Prestige ST artificial disc is available in the peer-reviewed literature (Mummaneni et al. 2007) and in the PMA Summary of Safety and Effectiveness submitted to the FDA (<http://www.fda.gov/cdrh/pdf6/p060018.html>). Both data sources were used in this analysis. The study was a multicenter (34 sites), nonblinded, randomized, controlled trial.

Inclusion criteria were DDD accompanied by neck pain at a single level between C3 and C7 confirmed by history and radiographic studies; presence of a herniated disc and/or osteophyte formation; at least 6 weeks of unsuccessful conservative treatment or signs of progression or spinal cord/nerve root compression with continued nonoperative care; no previous surgical intervention at involved level or planned procedures at involved or adjacent level; older than 18 years of age; preoperative NDI score greater than 30; preoperative neck pain score of greater than 20 on Neck and Arm Pain Questionnaire; and not pregnant.

Six-hundred twenty-five participants were randomized at each site on a 1:1 basis to ACDF (n=313) or AIDA (n=312). Of those randomized to ACDF and AIDA, 85% and 88% respectively,

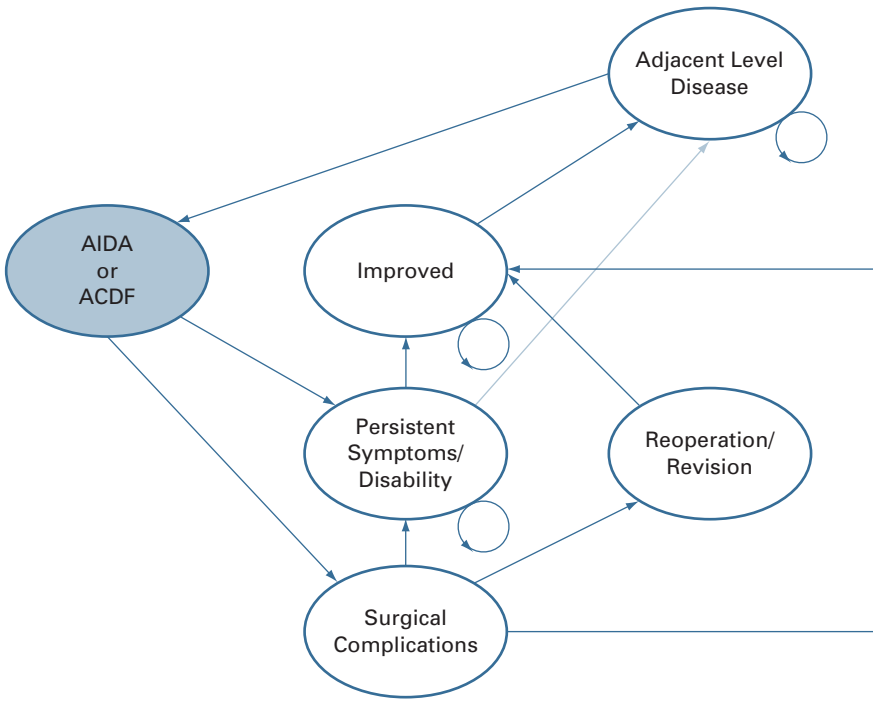


Figure 1. Relevant Health Outcomes (States) and Transitions for AIDA or ACDF

underwent surgery—265 ACDF using allograft bone and anterior cervical plate fixation and 276 receiving the Prestige ST artificial disc. Systematic differences (and statistically significant) between nonparticipants and participants in both study arms were described in the FDA submission. Among individuals randomized to AIDA, nonparticipants were less likely Caucasian, working, or smokers; among those randomized to ACDF, nonparticipants had lower neck pain scores and more often were working.

Subjects were evaluated preoperatively (within 6 months of surgery), intraoperatively, and postoperatively at 1.5, 3, 6, 12, 24 months, and annually thereafter. Outcomes included the NDI (assessing pain/disability), neck pain, arm pain, patient gait, foraminal compression, general health status, patient global perceived effect, doctor's perception of results, radiographic parameters and overall success. Radiographic outcome parameters consisted of the functional spinal unit (FSU) height as well as evaluations of motion and fusion at the treated level for the investigational and control group, respectively. Adjacent level motion was also assessed. At each timepoint, primary and secondary clinical and radiographic outcome parameters were evaluated.

Primary Study Endpoints and Success Criteria

The primary composite outcome, termed “overall success,” included the following individual endpoints: pain and functional disability as reflected by the NDI; neurological status; implant- or surgery-associated adverse events; secondary surgical interventions; and, initially a radiographic spinal unit height determination (subsequently removed). The composite “overall success” occurred when all the following component endpoints were reached:

1. An improvement (reduction) of at least 15 points from the baseline NDI score. (Details on the NDI are presented in the Background of this Assessment.)
2. Maintenance or improvement in neurological status based on 3 parameters (sensory, motor, reflex). No detail was provided on their measurement.
3. No serious adverse event classified as implant-associated or implant/surgical procedure-associated.

4. No additional surgical procedure, for example revision to ACDF or removal of the device, which would be classified as “failure.”

As noted, the original trial protocol included maintenance of FSU height as a component endpoint (not decreasing more than 2 mm after 6 weeks following surgery), because of the difficulty evaluating due to anatomical interference with the radiographic image, an alternate overall success determination was reported made based on the above criteria excluding height maintenance.

Statistical Analysis

The trial was a noninferiority design with a 10% margin—the success rate of the Prestige group was hypothesized to be not lower than ACDF by more than 10%. While 1.5-, 3-, 6-, 12-, and 24-month results were reported, our focus is the 24-month follow-up. The FDA submission reported less complete follow-up than Mummaneni et al. (2007), accordingly the latter results are reported here.

Prestige ST Study Results

Preoperative Characteristics

Table 1 shows similar demographic and clinical characteristics of the control and experimental arms. The average patient age was 43.3 and 43.9 years in AIDA and ACDF arms, respectively and 46% were male. Approximately one third of patients used tobacco at the time of enrollment; alcohol use was more frequently reported in the ACDF arm (53% versus 44%). Detailed preoperative neurological findings, such as weakness or reflex changes were not described.

Surgical Results

Operative time was somewhat shorter with ACDF (1.4 versus 1.6 hours), blood loss was similar (60 cc with AIDA, 58 cc with ACDF), as was length of stay (1.0 and 1.1 days for ACDF and AIDA, respectively). External orthoses were used in 59% of ACDF and 31% of AIDA patients.

Clinical Outcomes

At 24 months, follow-up in the AIDA arm included 80% of those undergoing surgery (71% of randomized patients); follow-up in the ACDF arm included 75% of those undergoing surgery (63% of randomized patients). Mean NDI improvement and success rates were

Table 1. Prestige ST Cervical Disc IDE Clinical Trial: Preoperative Characteristics

Demographic Characteristics	Prestige Disc	ACDF
Randomized and Treated	276	265
Mean Age (range)	43.3 (25-72)	43.9 (22-73)
Males	46%	46%
Tobacco use	34%	35%
Alcohol use	44%	53%
Workers' compensation	12%	13%
Symptom duration		
<6 weeks	21 (8%)	15 (6%)
6 weeks to 6 months	81 (29%)	89 (34%)
>6 months	174 (63%)	161 (60%)
Spinal level treated		
C3-C4	7 (2%)	10 (4%)
C4-C5	14 (5%)	15 (6%)
C5-C6	143 (52%)	149 (56%)
C6-C7	112 (41%)	91 (34%)
Baseline Scores (mean ± SD)		
NDI	56 ± 15	56 ± 16
Neck Pain Score	68 ± 23	69 ± 22
Arm Pain score	59 ± 29	62 ± 28
SF-36 PCS	32 ± 7	32 ± 8
SF-36 MCS	42 ± 12	43 ± 12
MCS: Mental Component Summary; NDI: Neck Disability Index; PCS: Physical Component Summary; SD: standard deviation; SF-36: 36-Item Short Form Health Survey		

similar between groups. As measured by the composite endpoint, AIDA was superior to ACDF (Table 2). The only component endpoint showing superiority was neurological status superiority was shown for the neurological status endpoint. At 24 months, secondary outcomes were similar and none was superior in either arm.

Device-Related Adverse Events and Functional Measures

Secondary surgical procedures (Table 3) appeared more common following ACDF but mutual exclusivity of categories was not specified. Consequences of secondary procedures were not completely detailed. For example, 4 of 5 patients undergoing artificial disc removal reportedly suffered persistent radiculopathy; like consequences of secondary procedures in the ACDF arm were not reported. Other adverse events occurred with similar frequency.

Four of the 5 ACDF revisions were for adjacent level disease. Overall, secondary surgeries for adjacent level disease were more common following ACDF (3.4% versus 1.1% respectively, $p = 0.07$, χ^2 1 df).

Nearly all ACDF patients (97.5%) experienced radiographic fusion at 24-month follow-up. Mean cervical neck angular motion (7.59 degrees) was maintained at preoperative levels (mean 7.55 degrees) at the surgical level in arthroplasty patients and restricted as expected in ACDF patients. Radiographic evidence of adjacent-segment degeneration was not assessed, nor was information available from the clinical study on wear and disc space debris.

Study Quality

Trial quality was rated poor (Appendix B) due to systematic differences between the randomized and treated groups and unclear blinding of neurological assessments.

Table 2. Prestige ST Cervical Disc IDE Clinical Trial: Clinical Outcomes

24-Month Outcomes	Prestige ST Disc n=276	ACDF n=265
Primary		
NDI mean improvement (0–100 scale)	36	34
NDI success (≥ 15 improvement)	84%	81%
Neurological Status Maintained or Improved	93%	84%
Overall Success ^a	79%	68%
Secondary		
SF-36 PCS Improvement	13.1	11.8
SF-36 MCS Improvement	7.4	7.5
Neck Pain Score Improvement	53	54
Arm Pain Score Improvement	46	49
Return to Work	75%	75%
^a p=0.004 superiority No measure of variability reported for means Reported p-values for superiority are not cited here due to lack of adjustment for multiple comparisons and being 1-sided		

Table 3. Prestige ST Cervical Disc IDE Clinical Trial: Device-Related Adverse Events and Secondary Surgical Procedures at 24 Months

Adverse Events	Prestige n=276 (%)	ACDF n=265 (%)
Neurological	4 (0.4)	1 (0.4)
Anatomic/technical difficult	1 (0.7)	0 (0.0)
Infection	2 (0.7)	0 (0.0)
Neck and/or arm pain	1 (0.4)	0 (0.0)
Respiratory	1 (0.4)	0 (0.0)
Dysphagia/dysphonia	2 (0.7)	3 (1.1)
Vascular	2 (0.7)	1 (0.4)
Other pain	2 (0.7)	2 (0.8)
Gastrointestinal	0 (0.0)	2 (0.8)
Other	2 (0.7)	2 (0.8)
Any	17 (6.2)	11 (4.2)
Secondary Surgical Procedures		
Revisions	0 (0.0)	5 ^a (1.9)
Hardware removals (elective and nonelective)	5 ^b (1.8)	9 ^c (3.4)
Supplemental fixations	0 (0.0)	8 ^d (3.0)
Secondary surgery for adjacent-segment disease	3 (1.1)	9 (3.4)
^a 4 of the 5 classified as revisions involved adjacent level fusion ^b 4 of the 5 suffered persistent postoperative radiculopathy ^c 2 elective, 7 non-elective ^d 9 procedures in 8 patients		

ProDisc-C IDE Clinical Trial

Methods. Study design, outcomes, and conduct were nearly identical to the Prestige ST trial: general inclusion and exclusion criteria, follow-up schedule, primary study endpoints, success criteria, noninferiority design and margin (10%) (Murrey et al. 2008). Differences included: 1) a 60-year age limit for participants, 2) no specified arm pain severity score for eligibility, 3) addition of a 20-point NDI success criteria outcome, 4) randomization specified in a block size of 4 and, 5) to avoid withdrawals from foreknowledge of procedure, participants were blinded to study arm until following surgery.

The study was a multicenter (13 sites and 13 surgeons), randomized, controlled trial including 209 patients (ProDisc-C, n=105; ACDF, n=106). There was no report of any withdrawals following randomization. At 24 months, follow-up rates were 98% in the ProDisc-C and 95% in the ACDF arms, respectively.

Preoperative Characteristics

Reported demographic and clinical characteristics were similar between arms (Table 4). Fewer than half were male, a third current smokers, and most employed. Baseline NDI, neck pain, and arm pain scores were similar to the Prestige trial. Baseline SF-36 scores were not reported.

Surgical Results

Operative times were 10 minutes shorter with ACDF; blood loss with ACDF was less (64 cc versus 84 cc); lengths of hospital stay were similar.

Clinical Outcomes

As reflected by composite endpoint (Table 5), outcomes with ProDisc-C at 24 months were noninferior to ACDF. Mean NDI improvement and success rates were nearly identical between groups. Secondary outcomes were likewise similar.

Table 4. ProDisc-C Cervical Disc IDE Clinical Trial: Preoperative Characteristics

Demographic Characteristics	ProDisc-C	ACDF
Randomized and Treated	103	106
Mean Age (SD)	42.1 (8.4)	43.5 (7.1)
Males	46%	49%
Current Smokers	33%	37%
Alcohol use	NR	NR
Employed	83%	85%
Spinal level treated		
C3-C4	3 (3%)	1 (1%)
C4-C5	10 (10%)	6 (6%)
C5-C6	58 (56%)	61 (57%)
C6-C7	32 (31%)	38 (36%)
Baseline Scores (mean ± SD)		
NDI	54 ± 15	52 ± 15
Neck Pain Score ^a	73	65
Arm Pain Score ^a	64	60
SF-36 PCS	NR	NR
SF-36 MCS	NR	NR

^a Interpolated from figure

MCS: Mental Component Summary; NDI: Neck Disability Index; PCS: Physical Component Summary; SD: standard deviation; SF-36: 36-Item Short Form Health Survey

Device-Related Adverse Events and Functional Measures

Secondary surgical procedures were more common in the ACDF arm (absolute difference 6.6%; 95% CI: 0.6–12.5%) primarily attributable to ACDF revisions (Table 6). Reasons for these revisions were plate subsidence, plate lift with dysphagia, two cases of neck pain and pseudoarthrosis, and one requiring additional level fusion. One patient (0.9%) in the ACDF arm and none undergoing AIDA underwent adjacent level fusion. Nonsurgical adverse events occurred at similar rates in both arms.

At 24 months, 90.2% of those undergoing ACDF and no secondary surgery experienced fusion. Mean range of motion in the ProDisc-C group at 24 months was 9.36 degrees.

Study Quality

Study quality was rated fair (Appendix B) due to lack of description of patient flow to correspond with analyses as well as unclear blinding of neurological exams.

Discussion

After 2 years' follow-up, neck disability index scores and overall success composite outcome results following AIDA were noninferior to ACDF—with either the Prestige ST or ProDisc-C disc). In both trials there was general consistency of results for primary and secondary outcomes. While the Prestige ST trial additionally concluded superiority for the composite outcome, it was most certainly attributable to including the problematic neurological component endpoint in the composite measure. Drawing conclusions requires considering two fundamental issues: 1) trial quality and 2) whether 2 years' follow-up can establish longer term noninferiority with sufficient decision certainty. Lastly, a related question, if AIDA is noninferior to ACDF, are other benefits (Kaul and Diamond 2006) provided by AIDA adequately compelling to adopt AIDA?

The Prestige ST trial was judged of poor quality due to systematic differences between the

Table 5. ProDisc-C Cervical Disc IDE Clinical Trial: Clinical Outcomes

24-Month Outcomes	ProDisc-C n=103	ACDF n=106
Primary		
NDI mean score	32 ± 7	20 ± 18
NDI success (≥15 improvement) ^a	80% ^a	78% ^a
NDI success (≥20 improvement) ^a	85% ^a	86% ^a
Neck Pain Score Change (mm VAS)	46	43
Arm Pain Score Change (mm VAS)	43	44
Neurological Status Maintained or Improved	91%	88%
Overall Success ^b	72%	68%
Secondary		
SF-36 PCS Improvement	81%	74%
SF-36 MCS Improvement	72%	69%
Neck Pain Score Improvement (mm VAS)	53	54
Arm Pain Score Improvement (mm VAS)	46	49
Employed	80%	83%

^a An apparent error as reported in manuscript

^b p=0.01 for noninferiority

Table 6. ProDisc-C Cervical Disc IDE Clinical Trial: Device-Related Adverse Events and Secondary Surgical Procedures at 24 Months

Adverse Event	ProDisc-C n=103 (%)	ACDF n=106 (%)
Infection	0 (0.0)	1 (0.9)
Neck and/or arm pain	2 (1.9)	1 (0.9)
Dysphagia/dysphonia	0 (0.0)	1 (0.9)
Dural tear	1 (1.0)	0 (0.0)
Plate subsidence/migration	0 (0.0)	2 (1.9)
Pseudoarthrosis	0 (0.0)	2 (1.9)
Any ^a	3 (2.9)	7 (6.6)
Secondary Surgical Procedures		
Revisions	0 (0.0)	5 (4.7)
Hardware removals (elective and nonelective)	2 (1.9)	0 (0.0)
Pain with pseudoarthrosis	0 (0.0)	1 (0.9)
Supplemental fixations	0 (0.0)	3 (2.8)
Total Secondary Surgical Procedures ^b	2 (1.9)	9 (8.5)

^a p=0.33
^b p=0.03

randomized and treated groups and unclear blinding of neurological assessments. Fifteen percent randomized to ACDF and 12% to AIDA withdrew prior to surgery; characteristics of these patients differed from treated participants. While participants were randomized in a 1:1 fashion, neither details of randomization nor block size were specified to allow judging of allocation concealment. Although a per-protocol analysis was employed, the possible consequences of not employing an intention-to-treat analysis in the setting of a noninferiority trial are not straightforward. It is often asserted per-protocol analyses in noninferiority trials are conservative (Ebbutt and Frith 1998; Garret 2003), but the methodological literature is inconsistent. For example, Brittain and Lin (2005) found per-protocol analyses among 20 noninferiority trials submitted to the FDA were not conservative. Accordingly, while the absence of an intention-to-treat analysis is noted in the quality rating (Appendix B), the direction of potential bias on the noninferiority findings cannot be assumed. The ProDisc-C trial quality was rated as fair, owing to omission of some details, but such a rating is generally acceptable. The randomization procedure

apparently prevented withdrawals seen in the Prestige trial, but details of patient flow (e.g., a CONSORT diagram) were not provided in either trial. Inability to mask patients and physicians to the study treatments could have some potential for bias results in favor of disc arthroplasty (Benzel 2007).

Still, limitations notwithstanding, both trial results can be considered generally similar—a notable exception being secondary surgical procedures for adjacent level disk disease. In the Prestige ST trial, 9 patients underwent secondary surgeries in the ACDF arm and 3 following AIDA for adjacent-level disease. In contrast there was a single secondary surgery for adjacent level disease in the ProDisc-C trial in the ACDF arm and none following AIDA.

A second issue is whether a 2-year follow-up is an adequate time horizon for ascertaining comparative outcomes. Precluded are conclusions about long-term natural history of device performance, durability, and revisability as well as rates of adjacent level disc degeneration. Performance and durability are particularly important given the relatively young age

(mid-40s) of the patients in the trial, who conceivably could outlive the disc lifespan. This point was underscored in the FDA approval condition that the manufacturer of the Prestige ST disc continue to follow the patients in the IDE trial for 7 years total and in addition perform a 5-year enhanced surveillance study to evaluate adverse events in a broader patient population. The 7-year follow-up period mandated by FDA is likely sufficient to evaluate device durability and adjacent-level DDD, which has been estimated to occur at a rate of about 3% annually during the first 10 years following anterior cervical fusion (Hilibrand et al. 1999). Similarly, in an early case series, Goffin et al. (2003) concluded that “at least 5 years of follow-up will be needed to assess the long-term functionality of the prosthesis and protective influence on adjacent levels.” No study has definitively established that adjacent-level degenerative disk disease subsequent to fusion is a consequence of altered spinal motion patterns, rather than just due to the natural progression of degenerative disk disease (Anderson et al. 2007; Levin et al. 2007). It is therefore unclear whether AIDA will reduce the risk for adjacent-level degenerative disk disease. A distinct concern is the potential difficulty of revising a failed implant (McAfee 2006). This is a critical issue, given potentially serious effects of device slippage or failure that would require revision surgery.

A final consideration in a noninferiority comparison is the ancillary benefits (Kaul and Diamond 2006) that would support adopting a new technology. The first of these is the preservation of range of motion that is lost with ACDF. It is plausible that maintaining range of motion will be accompanied by higher patient satisfaction and even quality of life—although those links have yet to be demonstrated. The Prestige ST trial suggested that return to work may be earlier following AIDA than ACDF (medians 45 versus 61 days, respectively, $p=0.09$). An earlier return to work was not reported in the ProDisc-C trial.

Finally, Riew et al. (2008) performed a post-hoc subgroup analysis of 111 participants from the Prestige ST trial with myelopathy. Although the subgroup analysis was not prespecified and therefore severely limited evidence, no advantage was found with the Prestige disc over ACDF. The authors also noted “...although short-term results of cervical disc arthroplasty appear encouraging, studies with at least five

to ten years of follow-up are required before cervical disc replacement can be viewed as a standard treatment for disc-based cervical myelopathy.”

In summary, evidence from trials of the Prestige ST and ProDisc-C discs do not sufficiently inform whether health outcomes with either device are as beneficial as following ACDF.

Summary of Application of the Technology Evaluation Criteria

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether artificial intervertebral disc arthroplasty as a treatment for DDD of the cervical spine meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

1. The technology must have final approval from the appropriate governmental regulatory bodies.

Two cervical disc arthroplasty products (Prestige ST and ProDisc-C Cervical discs) received U.S. Food and Drug Administration (FDA) marketing approval in July and December 2007, respectively. The discs are indicated in skeletally mature patients for C5-C7 disc reconstruction following single-level discectomy for intractable radiculopathy and/or myelopathy. The devices are implanted via an open anterior approach. Intractable radiculopathy and/or myelopathy should present with at least one of the following items producing symptomatic nerve root and/or spinal cord compression that is documented by patient history (e.g., pain [neck and/or arm pain], functional deficit, and/or neurological deficit), and radiographic studies (e.g., CT, MRI, X-rays, etc.): 1) herniated disc, and/or 2) osteophyte formation.

A third product (Bryan Cervical Disc) received an approvable decision by an FDA advisory panel July 17, 2007, but had not received final marketing approval at the time this Assessment was originally prepared. As this Assessment was in press, the Bryan disc received PMA approval from the FDA (May 12, 2009). The Bryan disc is intended for use in patients similar to those for whom the Prestige device

is indicated. As this Assessment excluded studies using any non-FDA-approved or precursor devices, evidence on the Bryan disc was not included in the original body of the Assessment; data on this device are included in Appendix C of this Assessment. The addition of these data does not change the conclusions of this Assessment.

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

Evidence derives from two randomized controlled trials designed to test noninferiority—one of the Prestige ST and the other of the ProDisc-C. The Prestige ST trial compared AIDA (n=276) with anterior plated ACDF using allograft bone (n=265); the ProDisc-C trial compared AIDA (n=103) with ACDF (n=106). The evidence is insufficient to support conclusions concerning the comparative effect of AIDA on health outcomes.

First, the evidence does not permit conclusions on the long-term performance of AIDA and adverse events. Device performance, durability, and revisability are key considerations for the relatively young population enrolled in these trials. The available evidence also is insufficient to permit conclusions as to whether or not AIDA affects the postsurgical development of adjacent-level DDD. In contrast, conclusions on the relative safety of cervical disc arthroplasty appear sufficiently supported in the short term.

Second, trial results demonstrated noninferiority for AIDA versus ACDF for the primary and

overall success composite outcome. In the Prestige ST trial, while superiority with respect to the neurological status was found, and thus for the composite including it, quantitative data on neurological status are not available and it is not known whether it was obtained by blinded examiners, precluding interpreting its clinical meaning and relevance. Further, the Prestige ST trial did not find better outcomes of AIDA in terms of the NDI, a clinically validated, multidimensional outcome measure of neck pain and disability caused by cervical DDD. Taken together, these uncertainties preclude determining the comparative effect of AIDA on health outcomes.

3. The technology must improve the net health outcome; and

4. The technology must be as beneficial as any established alternatives.

The evidence does not permit conclusions as to whether AIDA for the cervical spine improves net health outcomes or is as beneficial as established alternatives.

5. The improvement must be attainable outside the investigational settings.

Whether artificial disc arthroplasty for the cervical spine improves the net health outcome has not been established in the investigational setting.

Based on the above, artificial intervertebral disc arthroplasty for the treatment of patients with cervical degenerative disc disease does not meet the TEC criteria.

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Appendix A

Table A1. Cervical Disc Prostheses Under Investigation in the U.S.

Prosthesis (Manufacturer)	Implant Composition	Articulation Design	Bearing Surface	Bearing Constraint	Fixation	FDA Status
Prestige® LP (Medtronic)	Titanium-ceramic composite	Ellipsoid saucer	MoM	Semi-constrained	Primary – dual rails Secondary – endplate ingrowth	FDA IDE clinical trial enrollment complete
Porous Coated Motion (PCM®) (Cervitech)	Cobalt-chromium- molybdenum UHMWPE	Ball and socket	MoP	Semi-constrained	Primary – ridged metallic endplates Secondary – endplate ingrowth	In FDA IDE clinical trial enrollment
Kineflex C® Cervical Artificial Disc Implant (Spinal Motion)	Cobalt-chromium- molybdenum	Three piece, metal core	MoM	Unconstrained	Primary – central keel Secondary – endplate ingrowth	In FDA IDE clinical trial enrollment
CerviCore™ Intervertebral Disc (Stryker)	Cobalt-chromium- molybdenum	Saddle	MoM	Unconstrained	Primary – dual rails Secondary – endplate ingrowth	In FDA IDE clinical trial enrollment

IDE: investigational device exemption; MoM: metal-on-metal; MoP: metal-on-polyethylene; PMA: premarket approval; SS: stainless steel; UHMWPE: ultra-high molecular weight polyethylene

Appendix B

Table B1. Study Quality Rating

	Quality	Initial Assembly Comparable Groups	<80% Loss to Followup, Maintain Comparable Groups	Measurements Reliable, Valid, Equal	Intervention Comparable/ Clearly Defined	Appropriate Analysis of Results
Mummaneni et al. 2007	Poor	Y	Y	Unclear ^a	Y	Unclear ^b
Murrey et al. 2008	Fair	Y	Y	Unclear ^a	Y	Unclear ^c

^a Neurological exam not specified as performed by blinded examiner

^b Per protocol analyses. As noted in the text, in the setting of non-inferiority the potential biases accompanying per-protocol analysis, while often considered conservative, remains open to question. Accordingly, lack of intention-to-treat analysis was not considered a flaw as it would be in the setting of superiority.

^c Did not describe patient flow

Appendix C

BRYAN Cervical Disk Trial

The design paralleled the Prestige ST trial with randomization prior to surgery and similar inclusion and exclusion criteria and outcomes (Heller et al. 2009). All 582 eligible individuals (of 673 screened) agreed to randomization (290 to AIDA, 292 to ACDF). Eighty (27%) in the ACDF arm and 37 (13%) in the AIDA arm declined participation after randomization; there were 12 crossovers from each arm; one patient mistakenly underwent AIDA instead of ACDF; and 2 patients in the ACDF arm were not treated according to FDA protocol. While preliminary analyses presented to the FDA used a Bayesian approach (for details, see TEC Assessment [Vol. 22, No. 12] or the FDA website at <http://www.fda.gov/ohrms/dockets/ac/cdrh07.htm#orthopaedic>), published results of complete 24-month follow-up cited in this Appendix applied frequentist analyses.

Preoperative Characteristics

Table C2 shows demographic and clinical characteristics of the control and experimental arms—similar to Prestige ST and ProDisc-C trials.

Surgical Results

Operative time was somewhat longer with AIDA (2.2 versus 1.4 hours), blood loss similar (92 cc with AIDA, 60 cc with ACDF) as was length of stay (1.1 and 1.0 days for AIDA and ACDF, respectively).

Clinical Outcomes

Two-year follow-up data were available for 230 (95%) undergoing AIDA and 194 (88%) undergoing ACDF. The overall success outcome was achieved more often at 24 months after AIDA (82.6% vs. 72.7%) and there was a mean 4.1 point greater improvement in the NDI scores (Table C3). As measured by the composite endpoint, AIDA was superior to ACDF. At 24 months, neck pain scores were lower following AIDA, while other secondary outcomes were similar.

Device-Related Adverse Events and Functional Measures

Secondary surgical procedures (Table 3) occurred with similar frequency in both groups. During follow-up after AIDA there was 1 revision, 3 removals, and 2 reoperations; following ACDF, there were 3 removals, 1 reoperation, and 4 supplemental fixations. There were no reports of adjacent level disease. A detailed tabulation of device-related adverse events over the 24 months was not included in the published results; FDA documents covered only partial follow-up through 24 months.

Study Quality

Trial quality was rated fair owing to disproportionate losses (two-fold) between arms following randomization. Similar to the other trials, neurological assessments were also not reportedly blinded.

Discussion

The results parallel those of the Prestige ST and ProDisc-C and therefore, alter neither conclusions of this Assessment nor application of TEC criteria. With the caveat of differential losses between randomization and surgery, and implications for uncertainty, these results support similar outcomes following the two procedures at 24 months. However, as noted in the discussion, given the nature of disease, longer-term follow-up on device performance, durability, and revisability is needed to provide adequate decision certainty regarding equivalence of the Bryan disc to ACDF.

Table C1. Device Description

Prosthesis (Manufacturer)	Implant Composition	Articulation Design	Bearing Surface	Bearing Constraint	Fixation	FDA Status
Bryan® (Medtronic)	Titanium alloy Polyurethane	Biarticulating contained bearing	Metal on polyethylene	Semi-constrained	Primary – milled vertebral endplates Secondary – endplate ingrowth	FDA advisory panel recommended approval by vote of 7-1 (7/16/07) Final FDA approval May 12, 2009 (#P060023).

Table C2. Bryan Cervical Disc IDE Clinical Trial: Preoperative Characteristics

Demographic Characteristics	BRYAN Disc	ACDF
Randomized and Treated	242	221
Mean Age (range)	44.4 (25-78)	44.7 (27-68)
Males	64%	65%
Tobacco use	26%	24%
Alcohol use	8%	4%
Currently working	64%	65%
Symptom duration		
<6 weeks	NR	NR
6 weeks to 6 months		
>6 months		
Spinal level treated		
C3-C4	3 (1%)	0 (0%)
C4-C5	12 (5%)	17 (8%)
C5-C6	140 (58%)	110 (50%)
C6-C7	87 (36%)	94 (42%)
Baseline Scores (mean ± SD)		
NDI	51 ± 15	50 ± 16
Neck Pain Score	75 ± 20	75 ± 23
Arm Pain score	71 ± 20	71 ± 25
SF-36 PCS	33 ± 7	32 ± 7
SF-36 MCS	42 ± 12	45 ± 12
Neurological abnormality	99.6%	98.6%
MCS: Mental Component Summary; NDI: Neck Disability Index; PCS: Physical Component Summary; SD: standard deviation; SF-36: 36-Item Short Form Health Survey		

Table C3. Bryan Cervical Disc IDE Clinical Trial: Clinical Outcomes

	Bryan Disc n=242	ACDF n=221
24-Month Outcomes		
Primary		
NDI mean improvement (0–100 scale)	34.7 ± 20.5	30.6 ± 19.8
NDI success (≥15 improvement)	86%	79%
Neurological Status Maintained or Improved	94%	90%
Overall Success ^a	82.6% (95% CI: 77.1 to 87.3)	72.7% (95% CI: 65.8 to 78.8)
Secondary		
SF-36 PCS Improvement	15.3	14.5
SF-36 MCS Improvement	9.4	7.1
Neck Pain Score Improvement	52	44
Arm Pain Score Improvement	52	50
Return to Work	77%	74%
^a p=0.01 superiority 1-sided test		



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