



## ARTIFICIAL DISC REPLACEMENT FOR DEGENERATIVE DISC

### DISEASE OF THE LUMBAR SPINE

*A Technology Assessment*

#### INTRODUCTION

The California Technology Assessment Forum has been asked to update its review of the scientific literature on the safety and efficacy of artificial spinal disc replacement for the treatment of low back pain caused by lumbar degenerative disc disease.

This review will update the October 19, 2005 assessment of the Charité Artificial Disc ([www.ctaf.org](http://www.ctaf.org)) and assess the recently approved ProDisc L. Since the last review, additional details from the pivotal randomized clinical trial of the Charité disc have been published, as well as three randomized trials of lumbar spinal fusion for the same indication. The two devices will be reviewed independently.

#### BACKGROUND

##### Back Pain

Up to 40% of chronic low back pain has been reported to originate from the intervertebral disc <sup>1</sup>, but there is controversy surrounding its diagnosis and management. Low back pain caused by intervertebral disc disease may be insidious or sudden in onset. Pain is usually at the center of the back and may radiate to the buttocks or thighs. It is usually increased by sitting and improved by lying down. It is most commonly diagnosed by loss of disc height and water signal on MRI of the spine and may be confirmed by discography. The value of MRI and discography are controversial. In one study of asymptomatic patients, it was psychological distress, not MRI findings or pain with discography, that predicted future back pain.<sup>2</sup>

The usual treatments for low back pain include non-steroidal anti-inflammatory drugs, opioid analgesics and antidepressants. Physical therapy and cognitive behavioral interventions aimed at increasing patient confidence in their ability to do their usual daily activities may also be effective. For the minority of patients with persistent pain due to degenerative disc disease, treatment with spinal fusion is sometimes recommended.

##### Lumbar Spine Fusion Surgery for Degenerative Disc Disease

Patients with clear discogenic pain may benefit from complete surgical removal of the intervertebral disc and vertebral fusion. The goal of fusion is to alleviate pain due to motion at the joint. Measurable decreases in preoperative pain levels have been noted in over 80% of patients in various series of patients treated with spinal fusion.<sup>3</sup> A recent systematic review performed by the Agency for Healthcare Research and Quality's Duke Evidence-based Practice Center evaluated the utility of spinal fusion for this indication in detail.<sup>4</sup> They stress the importance of basing practice recommendations on high quality comparative trials because of the large effects of patient characteristics on response to therapy. They found four randomized clinical trials comparing one to two year outcomes of spinal fusion to non-surgical treatments of lumbar degenerative disc disease in patients with mean ages ranging from 40 to 45 years.<sup>5-8</sup> Two reported statistically significant differences in outcomes<sup>7, 9</sup> and two did not.<sup>5, 6</sup> (See the 1<sup>st</sup> four studies in Table 4 below for details) Neither of the two trials with statistically significant outcomes reported average improvements in the Oswestry Disability Index (ODI) of 15 points or greater, the minimum change considered to be clinically significant by the FDA. Improvements in the ODI ranged from nine to 15 points in the fusion arms of the trials and either 12 or 13 points in the conservative therapy arms, with one exception. In the trial with the largest difference in outcomes between arms, the conservative therapy arm only improved two points.<sup>9</sup> This trial has been criticized for the lack of a standardized physical therapy program directed at improving pain and function at the affected levels. Thus, it remains unclear whether spinal fusion offers any benefits over structured conservative therapy. The benefits, if any, are likely to be quite small.

Spinal fusions can be performed by an anterior or posterior approach. The majority of spinal fusion operations in the U.S. have been by the posterior approach, which in turn is comprised of three main techniques: a posterior lumbar interbody fusion (PLIF), a posterolateral gutter fusion surgery and a transforaminal lumbar interbody fusion (TLIF). In these procedures, the paraspinal muscles must be detached, thus potentially leading to paraspinal muscle weakness and atrophy in some patients. The PLIF and TLIF allow for placement of bone or a cage in the disc space. There are two types of anterior fusion procedures: the anterior/posterior lumbar fusion and the anterior lumbar interbody fusion (ALIF). The anterior approach preserves the paraspinal musculature and nerves. In addition, bone graft is placed in front of the spine and therefore receives more compression and may fuse more efficiently<sup>10</sup>. Risks of ALIF surgery include damage to large blood vessels, and in males, retrograde ejaculation in around one percent of cases.<sup>11</sup>

Fusing the spine is designed to decrease back pain by limiting the motion at a painful motion segment. Fusion usually occurs over a three to six month period (but can be up to 18 months) following surgery. Risks

associated with fusion include the risks of general anesthesia, infection, bleeding, neurologic complications and non-fusion. There are concerns that lumbar fusion may accelerate degeneration at other disc levels. Rigid immobilization of one spinal segment can lead to hypermobility of adjacent segments, which is thought to accelerate degenerative changes in the adjacent discs<sup>12-14</sup>. A recent systematic review of the topic found little evidence to support this popular hypothesis and suggested that progression of degenerative disease is the primary reason for adjacent segment disease, not spinal fusion.<sup>4</sup> However, artificial discs have been developed to allow removal of the diseased disc, while preserving normal range of motion at the disc.

### Charité Artificial Disc

The Charité Artificial Disc was developed to treat severe, chronic low back pain by replacing a damaged disc in the lower back with an artificial disc. It is made of two metallic endplates and a sliding plastic core. The disc was designed to restore disc space height, restore motion segment flexibility, prevent disc degeneration at adjacent segments, reduce or eliminate pain from motion or from nerve compression and improve the patient's functional activities. It was designed to have a life span of 40 years.

The surgical approach is typically through an anterior retroperitoneal route. Meticulous attention to implantation is required to ensure that the articulating surfaces of the endplates are parallel in order to restore normal biomechanics. Patient positioning is important so that radiographic confirmation of the implant position can be seen easily by the surgical team. A spine surgeon (either an orthopedic spine surgeon or a neurosurgeon) uses specially designed instruments to remove the damaged disc, create a space between two vertebrae for the implantation of the artificial disc and fit the Charité disc in between the two vertebrae. The disc replacement procedure is performed with the patient under general anesthesia and typically takes one to two hours to complete. During the U.S. clinical trials, the average hospital stay for patients was four days. Surgeons generally advise restriction of certain activities for a certain time period following the surgery and some surgeons may prescribe a back brace.

### Indications for Charité Artificial Disc Replacement

- Lumbar degenerative disc disease confirmed by the patient's medical history and an x-ray, MRI and/or other diagnostic tests
- Symptoms not relieved with at least six months of non-surgical treatment (pain medications, physical therapy, manipulation, ice and/or heat therapy, etc.)
- The damaged disc is located at either L4-L5 or L5-S1

### Contraindications for Charité Artificial Disc Replacement

- Multi-level disc degeneration
- Instability in the spine (such as spondylolisthesis, fracture or spinal tumor)
- Osteoporosis or osteopenia
- Prior spine surgery
- Pregnancy
- Facet joint arthritis

### ProDisc Artificial Disc

The ProDisc device has two cobalt chrome alloy endplates with an ultra-high weight polyethylene core that has greater constraints than the Charité core, but still allows for flexion, extension, lateral bending and rotation of the spine at the level of the implant.

### Indications for ProDisc Artificial Disc Replacement

- Lumbar degenerative disc disease confirmed by the patient's medical history and an x-ray, MRI and/or other diagnostic tests
- Symptoms not relieved with at least six months of non-surgical treatment (pain medications, physical therapy, manipulation, ice and/or heat therapy, etc.)
- The damaged disc is located at a single level between L3 and S1

### Contraindications for ProDisc Artificial Disc Replacement

- Multi-level disc degeneration
- Instability in the spine (such as spondylolisthesis > Grade 1, fracture or spinal tumor)
- Osteoporosis or osteopenia (T-score <-1.0)
- Bony spinal stenosis
- Pregnancy
- Involved vertebral endplate dimensionally smaller than 34.5mm in the medial-lateral and/or 27mm in the anterior-posterior directions
- Active infection of the spine
- Allergy or sensitivity to implant materials (cobalt, chromium, molybdenum, polyethylene, titanium)

## Technology Assessment (TA)

**TA Criterion 1:** The technology must have the appropriate regulatory approval.

On October 26 2004, the U.S. Food and Drug Administration (FDA) approved the CHARITÉ™ Artificial Disc (DePuy Spine, Inc., a J&J Company, Raynham, MA). This device is indicated for spinal Arthroplasty in skeletally mature patients with degenerative disc disease (DDD) at one level from L4-S1. These patients should have no more than 3mm. of spondylolisthesis at the involved level and should have failed at least six months of conservative treatment prior to implantation of the CHARITE Artificial Disc.

The PRODISC®-L Total Disc Replacement (Synthes Spine, Inc., West Chester, PA) received FDA approval on August 14, 2006. The PRODISC-L is indicated for spinal Arthroplasty in skeletally mature patients with DDD at one level from L3-S1. These DDD patients should have no more than Grade 1 spondylolisthesis at the involved level. Patients receiving the PRODISC-L Total Disc Replacement should have failed at least six months of conservative treatment prior to implantation of the PRODISC-L Total Disc Replacement.

TA Criterion 1 is met.

**TA Criterion 2:** The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The Medline database, Cochrane clinical trials database, Cochrane reviews database and the Database of Abstracts of Reviews of Effects (DARE) were searched using the key words artificial disc or Charité or ProDisc. These were cross-referenced with the keywords lumbar and human. The search was performed for the period from 1966 through January 2007. The bibliographies of systematic reviews and key articles were manually searched for additional references and references were requested from the device manufacturers. We also reviewed “related articles” in PubMed for each of the key clinical trials. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full. We focused on studies published since the last review, but have included summaries of the studies reviewed in the past when appropriate to provide context.

The updated search identified two new publications describing uncontrolled case-series of patients treated with the Charité disc, including one controversial description of patients with an average of 17 years of follow-up.<sup>15, 16</sup> In the prior assessment, one U.S. study<sup>17-19</sup> that randomized 305 patients was identified. Since the last review, additional details on the same trial have been published.<sup>20, 21</sup>

There have been multiple publications describing seven cases series<sup>22-31</sup> for the ProDisc total disc replacement and at least six publications describing the results of one randomized trial.<sup>32-37</sup>

Level of evidence: 1 and 5

TA Criterion 2 is met for both Charité and ProDisc.

### TA Criterion 3: The technology must improve the net health outcomes.

The benefits of treatment for low back pain include pain relief, decreased disability/restoration of function, cessation of narcotic therapy and return to work. The primary outcome measure used in most studies of back pain is change in the pain score as measured by a 100-point visual analog scale (VAS). Changes of 20 points or greater are generally considered clinically significant. Pain scores reported on a ten point scale were converted to the 100 point scale. Disability is usually measured by the 100-point Oswestry low back pain Disability Index (ODI); a change of 15 points or greater in the ODI is considered clinically significant by the FDA. Other short term outcomes commonly reported include quality of life, usually assessed with the SF-36, narcotic medication use and perioperative complications. Long-term outcomes include the same measures, plus the incidence of adjacent segment disease, rates of reoperation and return to work rates. Finally, for devices that are being placed primarily in 30-50 year old adults, long-term device failure rates represent an important outcome.

#### Case Series – Charité

The primary value of case series is initially to provide accurate estimates for rates of adverse events, long term harms and to identify subgroups that may benefit to a greater or lesser extent from the device. These aims require prospective, systematic collection of outcomes data, including adverse events, with nearly complete follow-up.

Putzier et al. described the clinical and radiographic results for 71 consecutive patients treated with the Charité disc between 1984 and 1989. Follow-up information was available for 53 patients (75%). The average follow-up was 17.3 years (range 14.5-19.2 years). The patients' mean age was 44 years at implantation of the device and 62% were women. The average ODI score at follow-up was 42 and the average VAS pain score was 48. No change scores or baseline scores were presented. The most remarkable finding was that 23% (12/53) of patients went on to surgical fusion due to implant failure, and an additional 60% (32/50) had spontaneous fusion at the level of the artificial disc. Only 17% (9/53) of patients treated with the Charité artificial disc retained joint mobility in long term follow-up. The reasons for surgical

fusion included artificial device fracture in seven patients, subsidence in three patients, device dislocation in one patient, and intolerable pain in one patient. The authors do note that there was no adjacent segment disease among the nine patients with preserved motion at the affected level, but that overall 17% of patients had significant degenerative changes at adjacent levels. The report has been strongly criticized by others in two four-page long letters to the editor.<sup>38, 39</sup> The primary criticism focuses on the learning curve required when developing any new device and points to rapid declines in complications following hip arthroplasty over time. The critics also point out that the device has evolved with cobalt chromium alloys now replacing the original stainless steel endplates. Additionally, devices with a wider range of sizes that allow for more precise fitting of the device are likely to result in better outcomes today.

One other case series<sup>40</sup> discussed in the prior review reported long-term outcomes on patients who received disc replacement with the third generation Charité artificial disc. Seven patients of the 107 in the series were not available for evaluation: six had moved away and were unable to be contacted; the seventh died from lung cancer. The remaining 100 patients were an average of 40 years old at the time of surgery (range 24 to 51 years) and 59% were women. The average length of follow-up was 11.3 years and all patients were followed for at least ten years. Among the 95 patients who had not retired, 87 (92%) returned to work after the surgery. Radiologically, no subluxation of the prosthesis or the polyethylene core was found. Long-term complications included the need for secondary fusion in five patients, symptomatic facet joint disease in four patients, periprosthetic ossification in two patients, adjacent level degeneration in two patients and subsidence in two patients. The primary value of this new report is that it gives some evidence in support of the long-term viability of the Charité artificial disc. The number of device failures and additional surgeries appears to be low. Unfortunately, it is unclear from the report whether there was any systematic follow-up for clinical outcomes and no data was given on when the outcomes presented were measured. Standard outcome measures, such as the VAS and ODI, were not reported. Complications were described in detail, but it was not possible to evaluate how many patients were free from complications during follow-up. These results also suggest that the high rate of spontaneous fusion seen in the earliest patients treated with the Charité disc may be less of an issue with newer devices and more surgical experience.

The other new case series was small (n=13) and focused primarily on the biomechanical effects of Charité disc replacement on the facet joints.<sup>16</sup> Three patients experienced post-operative complications (23%): one patient with ileus and two patients with sympathetic nerve dysfunction related to the anterior approach. At one-year follow-up, the ODI score had decreased from 53 to ten and the VAS back pain had decreased from 68 to 16. Subchondral bone density, a surrogate marker for joint loading, did not increase for any

patients during the first year after surgery. Significant decreases were noted in 77% of patients (10/13) at the level of the implant and in approximately 50% of patients when adjacent segments were analyzed. The authors note that these changes may reflect decreased load on the facet joints after implantation of the artificial disc, though the lack of controls limits the strength of the conclusion.

### Randomized Clinical Trials – Charité

The essential data from the only randomized trial of the Charité artificial disc was published in 2005<sup>18, 19</sup> and was accompanied by two commentaries<sup>41, 42</sup>. Since that time, two additional articles have been published evaluating the association between surgical volume and clinical outcomes among patients within the trial<sup>21</sup>, and describing the type and frequency of reoperations for patients treated as part of the trial.<sup>20</sup> The study recruited 375 patients at 14 spine centers in the U.S. The initial five patients treated with an artificial disc at most centers (71 patients) were considered training cases and were not included in the randomized comparisons. 205 patients received the Charité lumbar artificial disc and 99 patients received the control surgery (ALIF with BAK threaded fusion cages and bone graft). Participants were an average of 40 years old and most were Caucasian (90%). There were trends towards the control group having more women (56% vs. 45%,  $p=0.09$ ), being heavier (82 kg vs. 78 kg,  $p=0.03$ ) and having a lower baseline activity level (6% vs. 17% moderate or active,  $p=.06$ ), although only weight impacted statistical significance. The majority of the patients were treated at the L5-S1 level (69%). Follow-up was comparable and good in both groups. At two years, follow-up was available for 92% of patients randomized to the artificial disc and 89% of patients in the fusion group.

Clinical and radiologic outcomes were described in detail. The primary outcome was “clinical success,” defined as patients meeting all of the following four criteria: at least 25% improvement in the ODI score at 24 months, no device failure, no major complications and no neurologic deterioration. A strict intention-to-treat analysis was used. Clinical success at two years was attained by 57% of patients randomized to the artificial disc and 46% of patients in the fusion group ( $p<0.0001$  by one-sided Blackwelder non-inferiority test;  $p=.087$  by two-sided Fisher exact test).

For both patient groups, the VAS and ODI scores improved significantly after surgery ( $p<0.001$  at all time points). The mean ODI score decreased from 51 to 26 at two years (-25) in the artificial disc group and from 52 to 30 (-22) in the fusion group. The change scores did not differ between groups ( $p=0.27$ ). However, the percentage of patients experiencing at least a 25% reduction in ODI was greater in the Charité group (64% vs. 50%,  $p=0.04$ ). Similarly, the VAS score decreased from 72 to 31 at two years (-41) in the Charité group and from 72 to 37 (-36) in the control group. The VAS change scores were not different between groups at two years ( $p = 0.11$ ). However, improvements in both the ODI and VAS were more rapid in the artificial disc



group than in the fusion group: the differences between groups for both the ODI and VAS were statistically significant at six weeks ( $p=0.02$ ) and remained significant through the 12 month evaluation ( $p=0.04$ ). At 24 months, more patients in the artificial disc group reported being satisfied with their treatment (74% vs. 53%,  $p=0.001$ ) and would have the same treatment again (70% vs. 50%,  $p=0.006$ ).

Other clinically relevant outcomes were reported. Narcotic use was lower in the artificial disc group (72% vs. 86%,  $p=.008$ ). However, narcotic use at the 24-month follow-up remained remarkably high (64%), even in patients receiving an artificial disc who were categorized as a “clinical success.” Improvements in employment rates were low in both groups. Before surgery, 53% of the artificial disc group and 58% of the control group were employed. Twenty-four months after surgery, 62% of the artificial disc group and 65% of the control group were employed.

Placement of the disc was assessed radiographically. Most of the subjects had ideal placement of the artificial disc (83%), but 11% had suboptimal placement and six percent had poor placement. Clinical outcomes correlated with the technical accuracy of surgical placement. Both improvements in the ODI and pain VAS were better in patients with ideal placement ( $p<0.05$  for both).

The findings in favor of the Charité device may be biased due to the lack of blinding. The primary outcome measures were subjective, based on patient self-report of pain and disability. The participants may have been led to believe that the new device was better. They were participating in a trial of a new technology with a two to one randomization design in favor of the new device. This suggests that the high likelihood of receiving the new device may have attracted patients to the trial. Those patients who were randomized to the artificial disc were likely to be delighted, while those randomized to standard therapy were likely to be disappointed.

Two additional articles<sup>41,42</sup> that comment on this randomized clinical trial were published in the same issue of *Spine*. Both expressed significant reservations about the study. The first commentary<sup>41</sup> argues that the reference procedure, anterior fusion with BAK cage, has fallen out of favor among surgeons because of frequent failures and, thus, gives an inappropriate control group. Dr. Mirza points out that the clinical success rate was low for both groups in the trial and that narcotic use was common even among patients who met criteria for “clinical success”. He notes that data from the FDA website indicate that 39% of patients in the artificial disc group had less than five degrees of motion at the implantation site, which is within the FDA’s definition of fusion. He concludes that “contrary to optimistic marketing, the data provided to the FDA and published in this issue of *Spine* argue for caution by patients and surgeons.”

Zindrick et al.<sup>42</sup> also question whether the BAK cage with iliac crest bone graft is the optimal comparison group by today's standards. They express concern that sub-optimal placement of the artificial disc, which occurred in 17% of patients, would result in abnormal loading of the facet joints and other aspects of the spinal structure. This may lead to poor short-term outcomes, as noted in the study report<sup>19</sup>, as well as increased degeneration over time. They also express concern about potential bias in outcomes due to patient expectations that the Charité artificial disc was better than standard fusion. Their greatest concern was that two year follow-up was too short to fully assess harms from particle debris and to assess whether the artificial disc offered any advantages over fusion in terms of slowing degeneration at adjacent levels of the spine. They conclude that surgeons should "proceed cautiously in incorporating this new technology into their clinical armamentarium."

In a separate publication,<sup>20</sup> the authors describe the reoperation rates in greater detail for the 205 patients randomized to the Charité disc, the 99 patients randomized to fusion, the 71 nonrandomized cases receiving the Charité disc that formed the training set in preparation for the trial, and an additional 313 continuing access cases who received the Charité disc at the randomized trial centers after completion of accrual for the study. All patients had at least two years of follow-up. It is interesting to note that the reoperation rate after receipt of the Charité disc in the continued access group (11%, 34/313) was higher than the rate observed in the randomized trial (6%, 13/205). Similarly, the time to reoperation among patients in the continued access group (193 days) was less than half the time observed in the clinical trial (476 days). This suggests that either patient selection or the quality of care was not as good following the clinical trial, even in the hands of experienced surgeons working with experienced staff at the clinical trial sites. It is also important to note that the continuing access cases all had a shorter average length of follow-up than the clinical trial patients, as they accrued only after the clinical trial was closed. With equal length of follow-up, the difference in the observed reoperation rates are likely to be even larger. The authors lumped the 589 patients receiving the Charité disc together and report a summary reoperation rate of 8.8% (53/589), compared to 10.1% (10/99) for patients randomized to fusion. Among the Charité cases, 24 underwent a repeat anterior approach procedure: 22 had successful removal of the original device and seven were revised with a new Charité disc. As expected, complications during repeat anterior surgeries were higher than in the original surgery. For example, the rate of great vessel injury was 3.6% in the clinical trial, but was 16.7% in the 24 patients who underwent anterior revision. The reasons for repeat surgery following placement of the Charité disc included device migration (24/589), persistent back pain (14/589), iatrogenic neurologic complications (14/589), and unrecognized preoperative instability (5/589). It is worth noting that the reoperation rates reported in this publication are already higher than those reported in the

ten year case-series of Lemaire et al,<sup>40</sup> suggesting that the results from that case series are likely to be overly optimistic.

The investigators also evaluated whether individual surgeon volume ( $\geq 15$  cases vs.  $< 15$  cases), institutional volume ( $\geq 15$  cases vs.  $< 15$  cases), or individual surgeon experience (first five cases vs. later cases) influenced outcomes. Mean operating time and mean length of hospital stay were significantly shorter for high volume surgeons, high volume institutions and in comparison to earlier cases in the experience of individual surgeons. There were trends towards fewer device failures and better patient outcomes (measured by VAS and ODI) for the same three groups, although complication rates tended to be higher. For the surgeons, there were significantly fewer complications (76% vs. 90%,  $p < 0.01$ ), significantly few neurologic complications (16% vs. 34%,  $p = 0.002$ ) and fewer device migrations (0.5% vs. 5.6%,  $p = 0.02$ ) for patients treated in the randomized trial compared to those treated during the training prior to the trial. This supports the general thesis that complications should decrease with time and that outcomes should improve, although if many surgeons offer the Charité device, no individual surgeon or institution may have enough cases to maximize the potential benefits from the device.

### Harms

Harms related to placement of the artificial disc have been poorly described in the published literature. In addition to usual perioperative complications, like myocardial infarction and venous thromboembolic disease, important complications with the anterior approach to the spine include vascular injury and damage to the paraspinal sympathetic chain. These risks may be increased with this procedure due to the instrumentation needed to restore disc space height and the need to precisely position the artificial disc.

A Dutch group <sup>43</sup> described the possible short- and long-term unsatisfactory results of disc prosthesis surgery. They note that most patients receiving artificial discs are between the ages of 30 and 50 years. In these active patients, complications can be expected to increase with longer follow-up, similar to total joint replacements in the extremities. They report a series of 27 patients who presented to a tertiary university referral center with unsatisfactory results or complications after Charité disc replacement. Their mean age was 40 years (range 30-67 years) at the time of operation. The mean time from disc replacement surgery was 53 months (range 11-127 months). Early complications were as follows: in one patient, an anterior luxation of the prosthesis after one week necessitated removal and cage insertion, which failed to unite. In another patient with prostheses at L4-L5 and L5-S1, the prosthesis at L5-S1 dislocated anteriorly after three months and was removed after 12 months. Abdominal wall hematoma occurred in four cases. Retrograde

ejaculation with loss of libido was seen in one case and erection weakness in another case. A temporary benefit was experienced by 12 patients, while 14 patients reported no benefit at all. Main causes of persistent complaints were degeneration at another level in 14, subsidence of the prosthesis in 16 and facet joint arthrosis in 11. A combination of pathologies was often present. Slow anterior migration was present in two cases, with compression on the iliac vessels in one case. Polyethylene wear was obvious in one patient 12 years after operation. In eight cases, posterior fusion with pedicle screws was required. In this relatively small group of patients receiving the Charité disc prosthesis, most problems arose from degeneration of other lumbar discs, facet joint arthrosis at the same or other levels and subsidence of the prosthesis. The first two complications represent the problems that the device was designed to avoid. The major difficulty with interpretation of this report is the lack of knowledge about the total number of artificial discs implanted. The implications are quite different if the 27 patients represent failures from 100 surgeries or failures from 10,000 surgeries.

As noted above, wear debris, a concern with polyethylene implants in the peripheral joints, is a concern with artificial intervertebral discs due to their proximity to the spinal canal and nerve roots. According to the manufacturer, in a long-term laboratory test of cyclical motion simulating >11 years of use, no wear debris particles were identified. As described in the French series, no unexpected complications were found in 100 patients at least ten years after placement of the device<sup>40</sup>. Finally, in the randomized clinical trial, complication rates were almost identical in the artificial disc and spinal fusion groups<sup>18</sup>.

#### Case series – ProDisc

The literature search identified seven cases series of patients, some of which were reported in multiple papers with overlapping patient populations.<sup>22-31</sup> All but the earliest report required a minimum of two year follow-up. The primary outcomes reported in the case series are summarized in Table 1; most reported dramatic significant improvements in both the ODI score and the VAS back pain score ( $p < 0.001$ ). Indeed, the average improvement for patients in these case series is greater than 50%. These improvements are much larger in both relative and absolute amounts than those reported in the randomized trials (see Table 4 below).

Table 1: Primary Outcomes in Case Series of the ProDisc Artificial Disc for Lumbar DDD

Study	Follow-up, yr	N	Baseline ODI	Change ODI	Baseline VAS	Change VAS	Good / Excellent results
Tropiano 2003	1.4	53	56	-42	74	-61	100%
Bertagnoli 2005	2.6	118	54	-25	75	-45	97%
Tropiano 2005	8.7	64	-	-	-	-	75%
Bertagnoli 2006	2.9	22	27	-13	80	-40	94%
Chung 2006	3.1	36	69	-48	75	-45	-
Leivseth 2006	2.0	41	48	-24	-	-	-
Siepe 2006	2.8	92	40	-21	70	-42	83%

ODI=Oswestry Disability Index Score; VAS = 100-point visual analog scale for back pain

\*P<0.05

Only one of the case series reported outcomes over a longer period than the clinical trial.<sup>29</sup> The investigators reported long-term follow-up on a consecutive series of 64 patients treated with the first generation ProDisc at either one or multiple levels. A total of 55 patients (86%) had long-term outcome data available for analysis. The average length of follow-up was 8.7 years (range 7.1-10.7 years). Neither the ODI nor VAS scores were obtained for patients. Back pain was assessed on a scale from 0 to 3: no pain (0) up to severe pain (3). A similar scale was used to assess impairment in activities of daily living: normal (0) up to severely limited or impossible (3). The 20-point modified Stauffer-Coventry score was used for overall assessment with higher numbers representing a better overall assessment. Sixty percent of patient (33/55) had at least a 70% improvement in their Stauffer-Coventry score, a level of improvement conventionally considered excellent. The mean Stuffer-Coventry score improved from 7.0 preoperatively to 16.1 in follow-up ( $p<0.0001$ ). Pain decreased from 2.7 to 1.3 ( $p<0.0001$ ) as did impairment in ADL's (2.0 to 0.78,  $p<0.0001$ ). Among the 24 patients working prior to surgery, 13 (54%) were still working, six had retired, and the remaining five were on disability or sick leave. Follow-up x-rays did not demonstrate any cases of device migration or mechanical failure and disc height was preserved when immediate post-operative and long term follow-up radiographs were compared. One case of spontaneous interbody fusion occurred during follow-up. Five patients had surgical complications associated with the anterior approach: one case of retrograde ejaculation, one venous thrombosis, one iliac vein laceration, and two incisional hernias. Five additional patients had post-operative radicular pain that the authors attributed to nerve root traction due to post-operative epidural fibrosis. The pain resolved within three months for all patients. The most important result of the study is the lack of device failure over almost nine years of follow-up. In contrast to the data on the early iterations of the Charité disc, there was only one case of spontaneous fusion.

### Randomized clinical trial – ProDisc

The primary results of the FDA trial are to be published in 2007.<sup>37</sup> The study was designed as a non-inferiority trial comparing the ProDisc artificial disc to fusion. A total of 38 surgeons at 17 sites participated in the study. Patients meeting the criteria listed in Table 2 were eligible for randomization. In brief, the patients were adults with single-level degenerative disc disease who had failed six months of conservative therapy. The investigators randomized 236 patients 2:1 to either the ProDisc-L (n=161) or circumferential fusion (n=75). The fusion procedure included anterior interbody fusion with femoral ring allograft and posterolateral fusion with pedicle screws and autologous bone graft. The primary outcomes in the trial were disability measured by the ODI, pain and satisfaction each measured on a ten point VAS, quality of life measured with the SF-36, neurologic success, device success and six measures of radiographic success. Neurologic success was defined as improvement or no worsening on sensory, motor, and reflex examination as well as the straight leg raise test. Device success was defined as the absence of reoperation for device repair, removal or supplemental fixation. The radiographic measures included device migration, device subsidence, disc height, fusion status, radiolucency, and flexion/extension range of motion. Overall success required improvements in all ten outcomes, including the ODI, SF-36, device, neurologic and radiographic measures. The sponsor and the FDA used slightly different measures of success; the FDA's definition was used throughout this review. Patients were evaluated at six weeks and three, six, 12, 18, and 24 months after surgery.

Table 2. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Age 18 to 60 years	Number of vertebral levels with DDD >1
Single-level DDD at L3- S1. Diagnosis of DDD	Lytic spondylolisthesis or spinal stenosis
Oswestry Disability Index score $\geq$ 40 (out of 100)	Degenerative spondylolisthesis of grade >1
Failed $\geq$ 6 months of conservative treatment	Prior fusion surgery at any vertebral level
Psychosocially, mentally, and physically able to fully comply with protocol, including adhering to follow-up schedule and requirements, and filling out forms	Vertebral endplates dimensionally smaller than 34.5mm in the medial-lateral and/or 27mm in the anterior- posterior directions
Willing to give written informed consent	Facet joint disease or degeneration
	Clinically compromised vertebral bodies at the affected level due to current or past trauma
	Osteoporosis: DEXA T score $\leq$ -2.5
	Back or leg pain of unknown etiology
	Paget's disease, osteomalacia or any other metabolic bone disease (excluding osteoporosis addressed above)
	Titanium, polyethylene, cobalt, chromium or molybdenum allergy
	Morbid obesity defined as a body mass index >40 or a weight more than 100lbs. over an ideal body weight
	Pregnant or planning pregnancy over the next 3 years
	Active infection – systemic or local
	Taking any drug known to potentially interfere with bone/ soft tissue healing (e.g., steroids)
	Rheumatoid arthritis or other autoimmune disease
	Systemic disease including AIDS, HIV, Hepatitis
	Active malignancy

There were no significant baseline differences between the two groups of patients. The mean age of the patients was 39 years and 51% were female. Follow-up was apparently excellent with 98% of patients completing the two year follow-up evaluation. The operative time (121 minutes vs. 229 minutes), estimated blood loss (204 cc vs. 465 cc), and hospital length of stay (3.5 days vs. 4.4 days) were all significantly lower ( $p < 0.001$ ) for patients randomized to the ProDisc arm of the study. Changes in the 100-point ODI favored the ProDisc group at all time points after randomization. At 24 months, patients in the ProDisc group had an average improvement from baseline of 46% (29/63 points), compared with a 36% improvement in the fusion group (23/63 points). Success, defined as at least a 15% improvement in the disability score, was achieved by more patients in the ProDisc group than in the fusion group (77% vs. 65%,  $p = 0.04$ ). Quality of life changes, as assessed by the SF-36, favored the artificial disc group with 79% improving at two years

compared with 70% of the fusion group (p=0.09). Neurologic success also favored the artificial disc group (91% vs. 81%, p=0.03). The overall success rate was better in the artificial disc group than in the fusion group (53% vs. 41%, p=0.04).

Other clinically important outcomes were reported, but were not part of the primary outcome defining overall success. Visual analog scales for pain improved by an average of 39 points from baseline, to 24 months in the artificial disc group and by 32 points in the fusion group. Narcotic use was still common in both groups (see Table 3).

Table 3: Narcotic Use by Patients in the Trial

	Artificial disc	Fusion
Preoperative, all	84%	76%
24 months, all	NR	NR
- 24 months, "overall success"	39%	31%
- 24 months, no "overall success"	79%	76%

NR: Not reported

Device success was similar in the two groups (96% artificial disc, 97% fusion). Failures in the artificial disc group included four device migrations, one device inserted backwards and one patient requiring additional fixation due to unresolved pain. The reoperation rate was 3.7% for the artificial disc group and 5.4% for the fusion group.

Radiographic outcomes were better for the artificial disc for disc height preservation (100% vs. 93%, p=.003) and generally favored the artificial disc, though no other measures were statistically different between the two groups. Among the patients receiving an artificial disc who were not reoperated on by 24 months, there were three cases of device migration noted on x-rays and one case of subsidence. There were no cases of radiolucency, loss of disc height, or spontaneous fusion.

There were a number of methodologic limitations that diminished the quality of the trial. Randomization was performed in blocks of six, which allows prediction of the randomization status of every sixth patient prior to allocation. Thus, there is partial violation of the principle of allocation concealment. Blinding was not addressed in the report. The treated patients were not blinded, which can result in biased results for the self-reported, subjective outcomes, like the VAS for pain, satisfaction, and the disability scores. This is particularly a problem in trials of new devices because many patients agree to be randomized because they believe that the new device offers an advance in treatment alternatives. Patients randomized to the new treatment (ProDisc) are more likely to be satisfied with their randomization, while those randomized to the



older procedure (fusion) are more likely to be disappointed. There was no description of the flow of patients in the trial – no accounting for the number screened, the number eligible for randomization, whether patients received treatment as allocated, and the reasons for and timing of drop-outs. This raises important questions about the reported outcomes, even though follow-up appeared to be excellent. The authors report that follow-up at 24 months was similar for the disc and fusion groups (98.6% and 97.1%), but the percentage of patients with data for evaluation of the primary endpoint was only 91% and 88.5% at 24 months. No explanation is offered for this discrepancy. If the nine percent of patients with missing data in the artificial disc group are considered failures and the 11.5% in the fusion group considered successes, the overall success rate would favor fusion (approximately 44% in the artificial disc group vs. 51% in the fusion group). There was no description of the statistical methods used for the primary analyses and it was unclear whether the analysis was done using an intention-to-treat approach. Six patients were noted to have been treated off protocol, but no further explanation is given. Perhaps those six patients were randomized to fusion and refused treatment. This may explain the slight deviation from the 2:1 randomization: given 161 patients randomized to the disc, there should have been 80 or 81 patients randomized to fusion instead of the reported 75. Concerns like this arise because of the incomplete reporting of the methods and results in the published report.

## Summary

The case series suggest that outcomes following placement of the Charité device are similar to those reported in the literature from case series of lumbar fusion. However, selection bias and the lack of controls make such interpretation weak. The case series are most useful in providing some data on the types of complications that can be expected, though these are incompletely reported. The two case series with more than ten years of follow-up present conflicting pictures of the long term outcomes. The study with an average of 17 years of follow-up in patients treated with the earliest versions of the Charité disc suggested that long-term outcomes were poor, with the majority patients having either spontaneous or surgical fusion and most having significant residual pain and disability.<sup>15</sup> The ten year data reported by Lemaire<sup>40</sup> were much more optimistic and may reflect benefits derived from newer generations of the device and greater surgeon experience implanting the device. However, the reported reoperation rate in this case series was less than that reported in the recent clinical trial,<sup>20</sup> which suggests that the Lemaire results may be overly optimistic.

The randomized clinical trial of the Charité has been described in detail. Appropriate randomization and allocation concealment were used, follow-up was good through two years and a strict intention to treat analysis was used. However, no one was blinded in the study. The lack of blinding in a study with subjective

measures as the principal outcomes (self reported disability and pain) is a much more important potential source of bias in the results. There is no way to adjust for this potential bias. The VAS and ODI scores suggest a trend towards better outcomes with the artificial disc after two years of follow-up. However, no data is presented on development or progression of disc degeneration at adjacent levels, the main theoretical benefit from the improved range of motion afforded by the artificial disc. Adverse events appear to be comparable in the two groups. On balance, there was no trend towards increased device failure or other adverse events in the artificial disc and all clinical outcomes either were significantly better or showed a trend towards better outcomes in the artificial disc group, compared with the spinal fusion group at all time points over two years of follow-up.

If we accept that spinal fusion improves net clinic outcomes in patients with intractable pain from degenerative disc disease, the case-series and clinical trial data suggest that the use of an artificial disc, in the highly selected population meeting the inclusion and exclusion criteria of the trial, also improves net outcomes at two years. The major unknown is whether the hypothesized benefits of preservation of motion at the affected segment offset the potential harms from the poorly characterized long-term risks of device complications in patients expected to live 40 to 50 years after device implantation.

TA Criterion 3 is met for both Charité and ProDisc.

TA Criterion 4:           The technology must be as beneficial as any established alternatives.

There is controversy surrounding the established treatment for refractory symptoms from degenerative disc disease. However, since the publication of the meticulously performed and reported Swedish randomized trial<sup>9</sup>, many back specialists consider spinal fusion to be the standard treatment despite management of the patients in the control arm being left to the discretion of local providers. Perhaps because of this trial, all four of the U.S. trials of artificial disc replacement have spinal fusion as the control arm. Unfortunately, it is not clear that fusion is the treatment of choice. The three most recent randomized clinical trials of spinal fusion for the treatment of pain and disability due to degenerative disc disease compared fusion to structured programs of behavioral and physical therapy. The absolute differences in outcomes between the fusion and non-surgical arms were very small (Table 4) and, in one study, favored conservative management. Given the unequivocal, though relatively small, risks of poor outcomes from the general anesthesia required for the surgical procedures, and the relatively high risk of reoperation with either artificial disc, it is not clear that surgery offers any advantage over aggressive physical therapy and behavioral therapy. Furthermore, in one of the randomized trials, patients managed with physical therapy were less likely to fear physical activity and work and were more likely to return to work.<sup>6</sup>

Table 4: Primary Outcomes in Randomized Trials of Devices for Lumbar DDD

Study	Follow-up, yr	Arm	N	Baseline ODI	Change ODI	Baseline VAS	Change VAS
Fritzell 2001	2	Fusion	222	47	-11	64	-21
		Conserv.	72	48	-2*	63	-4*
Brox 2003	1	Fusion	37	41	-15	62	-23
		Conserv.	27	42	-12	64	-15
Fairbank 2005	2	Fusion	176	46	-13	NR	NR
		Conserv.	173	45	-9*	NR	NR
Brox 2006	1	Fusion	29	47	-9	65	-14
		Conserv.	31	45	-13	65	-15
Blumenthal 2005	2	Fusion	99	52	-22	72	-34
		Charité	205	51	-24	72	-41
Zigler 2007	2	Fusion	75	63	-23	75	-32
		ProDisc-L	161	63	-29	76	-39

ODI=Oswestry Disability Index Score; VAS = 100-point visual analog scale for back pain

The black bar separates the clinical trials of lumbar spinal fusion vs. conservative therapy (above the bar) from the trials comparing lumbar spinal fusion to implantation of an artificial disc.

\*P<0.05

Two randomized trials directly compared use of the artificial disc to spinal fusion (see details under TA Criterion 3). In one<sup>17-19</sup>, complication rates appear equivalent in the artificial disc and spinal fusion groups and two year clinical outcomes favored the artificial disc group; in the other<sup>37</sup>, two year clinical outcomes were significantly better in the artificial disc group. However, the long-term outcomes are still uncertain with these novel devices. For the Charité disc, the ten year results in the French series are reassuring,<sup>40</sup> but the 17 year results are quite worrisome.<sup>15</sup> The primary advantage over fusion offered by an artificial disc is the preservation of range of motion at the affected joint, which may not be preserved over time. Furthermore, evidence supporting a reduction in degeneration in adjacent discs is weak. It is also important to note that the reductions in disability and pain reported in the randomized trials is less than 50% of the patients' baseline pain. Most patients still have significant pain and disability two years after surgery. Given the clear risks and uncertain long-term benefits, neither artificial disc offers any advantages over established therapies. When put in the context of equivalent or nearly equivalent results with structured physical and behavioral therapy programs, it is not clear that possible benefits of disc replacement with an artificial disc outweigh the attendant surgical risks and the possibility of long-term device failure.

TA Criterion 4 is not met for either Charité or ProDisc.

TA Criterion 5: The improvement must be attainable outside the investigational setting.

The Charité artificial disc is currently used in disc replacement surgery in more than 30 countries throughout

Europe, Asia, North America, Africa and Latin America. According to the manufacturer, worldwide experience with this disc replacement device is now greater than 15,000 cases. However, there is clearly an important learning curve to surgery using the Charité disc and quality can fall off without diligent attention to patient selection and surgical technique, as was demonstrated in the experience of centers and surgeons involved in the U.S. clinical trial.<sup>20</sup> It is likely that similar issues apply to the ProDisc device, but there is less published data documenting this effect.

The Spinal Arthroplasty Society has set a goal of establishing standardized training programs for physicians prior to their using any new artificial disc replacement technology. It is intended that the training be similar to that required for participation in the FDA clinical trials. Once surgeons have undergone training as recommended by the manufacturer, they may be able to achieve results comparable to those obtained in the investigational studies, given that they perform a sufficient number of the procedures annually. Outcomes are likely to be better at high volume centers. However, until it is clearly demonstrated in investigational settings that the benefits of artificial discs outweigh both the short-term risks of surgery and the long term risks of device failure, we cannot conclude that such improvements are attainable in other settings.

TA Criterion 5 is not met for either Charité or ProDisc.

## CONCLUSION

Six case series have been published describing the clinical outcomes for 393 patients who received the Charité artificial disc. Satisfactory clinical outcomes were reported for 63% to 79% of patients, which is comparable to reported success rates for lumbar fusion. One of the case series reported data on 100 patients with at least ten years of follow-up: there were no late device failures or unexpected neurologic syndromes. However, uncontrolled case-series are the weakest form of evidence. In a second case series with 17 year follow-up on 53 of 71 recipients of early iterations of the device, 83% of the patients had either surgical or spontaneous fusion at the level of the artificial disc. These patients also reported significant ongoing pain and disability; although without a control group, it is impossible to assess whether they received some benefits from the device.

The data from the seven case series evaluating 426 patients who received the ProDisc device were also promising. Good to excellent results were reported for 75% to 100% of patients, with large reductions in pain and disability reported over two to three years of follow-up. In the one series reporting results over 8.7 years, there were no device failures and only one case of spontaneous fusion. No second surgeries were reported.

Data from the randomized clinical trial of 304 patients comparing the Charité artificial disc to ALIF and the BAK cage have been published in detail. While there were some methodologic flaws, the overall quality of the trial was good. Improvements in self-reported pain and disability scores favored the artificial disc, but were of borderline statistical significance and may have been biased due to lack of blinding. Complication rates were similar in the two groups. Neither group had excellent overall results: average reductions in pain and disability were less than 50% and most patients still required narcotics for pain two years after surgery. Furthermore, between eight percent and 10 percent of patients required a second surgery for continued symptoms or device failure. The authors stated the primary motivation for artificial disc replacement was to maintain range of motion in order to avoid initiating or accelerating degeneration in adjacent segments. Range of motion, as expected, was significantly greater in the artificial disc group. However, they explicitly state that adjacent level degenerative disease would not be detectable with just 24 months of follow-up and did not report any data on adjacent level disease. A significant number of patients in the trial required additional surgeries (6.3%) and this number increased to 10.9% for patients receiving the device at the same centers following completion of the randomized trial.

The randomized trial of the ProDisc artificial disc suffered from the same methodologic issues. The device was compared to circumferential fusion. At two years, patients in the ProDisc arm had statistically significant improvements in the ODI and the FDA definition of overall success, but the absolute differences were not large. Only 53% of patients in the ProDisc arm met criteria for overall success, and the difference between the change in disability scores for the two groups was only six points; a difference of 15 points is considered clinically significant.

In summary, randomized clinical trial evidence demonstrated that two-year outcomes for patients receiving artificial discs were not inferior to outcomes for patients treated with fusion, but pain and disability decrease less than 50%. Data from case series with longer follow-up were conflicting. These data need to be interpreted in the context of a patient population that is relatively young at surgery (average age 40 years), which means that the disc prosthesis must last 30 to 50 years. Furthermore, recent clinical trials suggests that outcomes with intensive physical and behavioral therapy are equivalent to those achieved with fusion. The artificial discs have never been directly compared to these interventions. As noted under TA criterion 4, despite the promising results of the two randomized trials, it is not clear that possible benefits of the artificial discs outweigh the attendant surgical risks and the possibility of long-term device failure.

## RECOMMENDATION

It is recommended that the use of the Charité artificial disc does not meet Technology Assessment Criteria 4 and 5 for safety, effectiveness and improvement in health outcomes when used to treat pain and disability from degenerative disc disease of the lumbar spine.

*The CTAF panel voted to accept the recommendation as stated.*

It is recommended that the use of the ProDisc artificial disc does not meet Technology Assessment Criteria 4 and 5 for safety, effectiveness and improvement in health outcomes when used to treat pain and disability from degenerative disc disease of the lumbar spine.

*The CTAF panel voted to accept the recommendation as stated.*

February 28, 2007

## RECOMMENDATIONS OF OTHERS

### Blue Cross Blue Shield Association (BCBSA)

The BCBSA Technology Evaluation Center Medical Advisory Panel reviewed this technology in February 2007 and found that criteria were not met.

### Centers for Medicare and Medicaid Services (CMS)

In 2006 CMS determined that lumbar artificial disc replacement with the Charité lumbar artificial disc is not reasonable and necessary for the Medicare population over 60 years of age.. There is no national coverage determination for Medicare beneficiaries 60 years of age or younger. There was no statement regarding the ProDisc noted.

### California Association of Neurological Surgeons (CANS)

The CANS provided a response to a request for an opinion statement which notes the following, in part:

“CANS is committed to innovation and providing state of the art care to our patients who suffer from spinal disorders. We remain committed to assuring that these procedures are safe and effective, our physicians are adequately trained to accomplish those goals, and that our patients have access to innovative and emerging technologies. We urge the California Technology Assessment Forum to favorably consider ADR.”

A representative was not available to participate at the meeting.

### California Orthopaedic Association (COA)

The COA has not taken a formal position on the use of this technology. A representative was not available to participate at the meeting.

### Spine Arthroplasty Society (SAS)

The SAS was invited to provide comment regarding the use of this technology. A representative was not available to participate at the meeting..

**ABBREVIATIONS USED IN THIS ASSESSMENT:**

ODI: Oswestry Disability Index

PLIF: Posterior Lumbar Interbody Fusion

TLIF: Transforaminal Lumbar Interbody Fusion

ALIF: Anterior Lumbar Interbody Fusion

FDA: U.S. Food and Drug Administration

DDD: Degenerative Disc Disease

DARE: Database of Abstracts of Reviews of Effects

VAS: Visual Analog Scale



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