

**Delamarter R, Zigler JE, et al. Prospective, Randomized, Multicenter Food and Drug Administration Investigational Device Exemption Study of the ProDisc-L Total Disc Replacement Compared with Circumferential Arthrodesis for the Treatment of Two-Level Lumbar Degenerative Disc Disease Results at Twenty-four Months. JBJS 2011;93:705-15.**

Design: Randomized noninferiority trial

Population/sample size/setting:

- 237 patients (134 men, 103 women, mean age 42) treated for degenerative lumbar disc disease at 16 sites across the US
- Eligibility criteria were degenerative disc disease at two contiguous levels from L3 to S1 with or without leg pain, minimum of 6 months of unsuccessful nonoperative treatment, and a minimum Oswestry score  $\geq 40$ 
  - o Disc disease defined as lumbar spine instability, loss of intervertebral disc height, scarring of the anulus, herniated nucleus pulposus, or vacuum phenomenon of the disc
- Exclusion criteria were greater than grade I spondylolisthesis, degenerative discs at more than 2 levels, previous fusion, or inability to comply with study protocol

Main outcome measures:

- 256 patients were originally randomized in a 2:1 ratio to either ProDisc (n=174) or to circumferential fusion (n=82)
- Patient evaluations were done preoperatively, then repeated at 6 weeks and at 3, 6, 12, 18, and 24 months postoperatively
  - o Each visit included neurological examinations (sensation, motor strength, reflexes) and radiographic exams (AP, lateral, flexion-extension, lateral bending views); also, work/recreation status and completion of Oswestry, pain VAS, and the SF-36
- Principal outcome measure was a composite end point at 24 months
  - o “Success” required *all* of the following
    - $\geq 15\%$  improvement in Oswestry from baseline
    - Improvement in SF-36 over baseline
    - Neurological status improved or maintained from baseline
    - No secondary operations to modify the implant/fusion site
    - Radiographic success: no radiolucency/loosening, no more than 3 mm of subsidence, migration, or loss of disc height
    - For ProDisc: range of motion improved or maintained from baseline
    - For fusion: no motion ( $<10^\circ$  angulation for both levels combined on flexion/extension)
- 19 of the 256 patients who were randomized were not treated with either intervention, leaving 237 who received either ProDisc or fusion
- 215 patients could be classified as successes or failures at the 24 month point, 148 from the ProDisc and 67 from the fusion group

- Mean operative time was shorter for ProDisc (160 min) than for fusion (273 min), and the length of hospital stay was also shorter (3.8 vs 5.0 days)
- For the composite end point, success was reported for 58.8% of the ProDisc patients and for 47.8% of the fusion patients; this met the prespecified non-inferiority group difference, which would have been met even if there had been a success rate in the fusion group which was 12.5% greater than for ProDisc
- Other outcomes at 24 months were also either superior or non-inferior in the ProDisc group: Oswestry, SF-36 physical component scores, and neurological success
- Reoperation was required in 4 of 165 ProDisc patients (2.4%), and was required in 6 of 72 fusion patients (8.3%); this was a significant advantage for ProDisc
- Both groups improved their pain VAS scores between baseline and 24 months; the ProDisc group by 43.3 mm and the fusion group by 36.7 mm; the difference was not significant
- The majority of patients in both groups were using narcotics at baseline, 69.1% in the ProDisc group and 63.9% in the fusion group
  - o At 24 months, there were fewer ProDisc patients using narcotics (36.1%) than fusion patients (59.3%)
- The majority of patients in both groups (about 80%) were working both at baseline and at 24 months, with no significant group differences in work status

#### Authors' conclusions:

- ProDisc-L is an appropriate alternative to lumbar fusion in patients with two-level degenerative disc disease
- The statistical endpoint for this study, which was used to define success in the two treatment groups, was designed for the FDA regulatory application process, and may not be clinically relevant for most patient outcomes
  - o Clinical relevance appeared in outcomes which were not specified by the FDA process; for example, a 15 point improvement in the Oswestry score was seen in 73.2% of ProDisc patients and in only 59.7% of fusion patients
- Lack of blinding has the potential to bias the results of the study
- Two years is too short a follow-up time to detect meaningful differences between ProDisc and fusion with respect to adjacent level disease

#### Comments:

- The statistical analysis appears to conform to standards for non-inferiority trials as specified by Blackwelder and elaborated by other authors
- The comparison group received 360° fusion, which is the only valid comparison which can be made
  - o The longer operating times and the longer length of hospital stay should be interpreted in this light, and less invasive fusion procedures may have shorter length of stay and less blood loss

- Because of the exclusion of patients in whom the benefits of fusion are likely to be greater (those with instability and slippage beyond grade I), this non-inferiority trial is being done in a patient population in which the established treatment has less proof of effectiveness, potentially making the ProDisc appear more effective than is warranted (Fleming et al 2011)
- The conclusions therefore are circumscribed to comparisons with circumferential fusion in patients without more than grade I slippage, and are to be interpreted cautiously
- The difference in opiate use in favor of ProDisc is of interest and possible relevance, even though it was not the prespecified outcome

Assessment: Adequate for evidence that two-level lumbar disc replacement is not inferior to circumferential fusion in patients with two-level degenerative disc disease 24 months after the operation

#### References:

Blackwelder WC. "Proving the Null Hypothesis" in Clinical Trials. *Controlled Clinical Trials* 1982;3:345-353.

Fleming TR, Odem-Davis K, et al. Some essential considerations in the design and conduct of non-inferiority trials. *Clinical Trials* 2011; 8: 432–439.

Kaul S, Diamond GA. Good Enough: A Primer on the Analysis and Interpretation of Noninferiority Trials. *Ann Intern Med.* 2006;145:62-69.

Piaggio G, Elbourne DR et al. Reporting of Noninferiority and Equivalence Randomized Trials: An Extension of the CONSORT Statement. *JAMA* 2006;295:1152-1160