State of Total Disc Replacement: Past, Present, and Future

Richard D. Guyer, M.D.

Disclosures

Guyer (a) Alphatec; (b) Spinal Kinetics, Spinal Ventures, Mimedix; (c) DePuy-Synthes Spine, K2M, Flexispine, Mimedix, Aesculap; Safe Orthopedics (d) DePuy-Synthes Spine, K2M, Paradigm Spine

Key: (a) royalties; (b) stock/options; (c) consulting/SAB; (d) Speaker/faculty; (e) Research; (f) Fellowship and related research; (g) other

Introduction

• Lumbar and cervical TDR
  – Have been the most studied spinal conditions with more than a dozen IDEs
  – Long history in US dating to 2000
    • Strong outcomes
    • Lower than expected adoption for Lumbar but excellent for Cervical
  – Promising future
**TDR Market Overview**

- Global market for non-fusion treatments to expand from $521M in 2014 to $749M in 2021
- Growth driven by cervical TDR due to:
  - Increasing availability of clinical efficacy data
  - Improving reimbursement environment
  - Rising prevalence of degenerative spine diseases
  - Industry’s aggressive efforts in physician training and DTC marketing
- Market underpenetrated at only 20% of procedures globally, less in the US despite regulatory clearances of devices

**TDR Market Overview**

- Europe has been dominant market for C-TDR until ~2013 due to less stringent regulatory approval process
- US is now, and will remain, dominant market for C-TDR through 2020 with increasing number of approved devices, improved reimbursement

**Looking first at Lumbar TDR:**

- Lumbar TDR has been used OUS since 1980s
  - We know a lot about the outcomes
  - Multiple studies, from multiple countries show good outcomes at 2, 5, >10 yr follow-up
  - Multiple FDA-regulated trials found TDR to be at least as effective as fusion and superior on some measures
US IDE Studies (Not a Comprehensive List)

- Charité approved 2004, removed from US market 9/2013 by DePuy due to poor sales and purchase of Synthes (ProDisc), not disasters!!
- ProDisc-L approved 2006
- activL – approved 6/2015
- Maverick – completed, patent issues
- FlexiCore – withdrawn by Stryker
- Kineflex-L – withdrawn by Spinal Motion
- Freedom – 3rd gen, polymer, not submitted
- L TDR – lateral insertion, aborted
- Triumph – posterior insertion aborted

TDR Design Types

- Ball and Socket
  - Semiconstrained
  - Unconstrained
- Viscoelastic
  - Elastomeric polymer

FDA Trial Data Published

- Charite vs. ALIF - 5 yr data
- ProDisc-L vs. 360 - 5 yr data
- Maverick vs. ALIF - 5 yr data
- Flexicore vs. 360 - 2 yr data
- Kineflex-L vs. Charité - 5 yr data
- activL vs. Charité or ProDisc-L - 2 yr data
  - 5 yr coming very soon
What Is Needed for Widespread Use of an Implant?

- Must establish:
  - Safety
  - Efficacy
  - Defined indications
  - Address cost
- Equally Important
  - Reimbursement
  - Surgeon perception

Safety

Multiple studies found a significantly lower re-op rate for TDR vs. fusion
- Others found rate lower or similar for TDR vs. fusion
- No randomized studies found a higher re-op rate for TDR

TBI Re‐operation Experience

- Consecutive series beginning with 1st TDR case in 2000 from IDE studies
- Included all TDR pts at least 2 yrs (longest 134 months) post-op and all pts who were fusion controls in randomized FDA IDE TDR trials
  - 1,058 TDR
  - 112 hybrid
  - 67 fusion

ISSLS, 2013
TDR: Effectiveness

- Lumbar FDA IDE trials:
  - 4 with 5 yr follow-up
  - 2 additional with 2 yr follow-up
- Multiple studies from Europe with >10 yr follow-up
- Multiple studies from Asia with 2-5 yr follow-up

All these studies have consistently reported maintained good outcomes throughout longest term follow-up.

FDA IDE trials found significant improvement by 6 wk post-op and maintained through 2 and 5 year follow-up with NO DEGRADATION.

Following are new additional lumbar TDR studies.
• DDD group (n=39): Axial LBP from DDD
• DDD+other group (n=15): DDD + >1 of the following: previously fused adjacent level, spondy, retrolisthesis, facet joint arthritis, lateral recess stenosis
• Mean follow-up 120.0 mo

Mean 10-yr Clinical Follow-up

• Significantly better outcomes in DDD vs. DDD+other dx group:
  – Success: 76.9% vs. 40.0%
  – Satisfaction: 87.2% vs. 60.0%
• 5 pts (9.3%) had revision fusion surgeries, all were DDD+other group
• Segmental ROM was well maintained in DDD group, but not in the other group

83 pts receiving M6 lumbar TDR (49 1-level, 43 multi-level)
• Prospective, post-market, multicenter registry study
• Significant improvement in VAS and ODI scores (p<0.05; ≥50% improvement)
• No device revisions or removals (no comment on other re-ops)
What’s New for Lumbar TDR and Updates

Patient-Specific Templating of Lumbar Total Disk Replacement to Restore Normal Anatomy and Function

- Used CT and finite element modeling to evaluate interaction of pt anatomy, implant geometry, and implant positioning with goal of maximizing ROM and outcomes
• TDR had statistically significantly greater improvement in back pain, ODI scores and pt satisfaction
  – Conclusions: differences in clinical improvement were not beyond generally accepted boundaries for clinical relevance
Meta-analysis of RCTs

- Purpose: Compare effectiveness and safety of TDR vs. fusion
- Searched Medline, Embase, Clinical, Ovid, BIOSIS and Cochrane registry of controlled clinical trials
- 7 relevant RCTs with total of 1,584 pts, 2 yr follow-up
- TDR more effective in ODI, VAS, hospital stay duration, greater willingness to choose the same operation again
- Differences not significant for op time, blood loss, complications, re-op rate or RTW rates

Rao, Arch Orthop Trauma Surg, 2014

Other Clinical Outcome

- One of the major potential clinical benefits of lumbar TDR is reducing the occurrence of adjacent segment degeneration
- Those of us involved in TDR from the beginning have been searching for this evidence as it is what has motivated our research
- But ASD is like old “Natural history vs Increased stress of fusion” or “Genetics vs Environment” arguments

ASD: ProDisc TDR vs. Fusion
The “Holy Grail” of lessened ASD finally!!!

- Δ ASD observed at 5 years in:
  - 28.6% of fusion patients
  - 9.2% of TDR patients

> 3 : 1 Difference

P<0.01

For each additional degree of motion at the TDR level, there was a decline in the rate of ASD (data from activL FDA trial).

ASD and ROM at TDR level: 5-yr Follow-up from Activ L

% of patients with ASD

ROM at TDR level

>0° >1° >2° >3° >4° >5° >6° >7° >8°

0% 2% 4% 6% 8% 10% 12%

Guyer, ISASS, 2017

ASD and Age at 5-yr Follow-up

% of patients with ASD

<40 yr old >40 yrs old

5.0% 19.6%

ASD significantly greater in older patient subset, p<0.01 (data from activL FDA trial data)

Guyer, ISASS, 2017

Reviewed 27 Class I and II fusion and TDR studies
- 314/926 fusion patients developed AgDD = 31%
- 31/313 TDR patients developed AgDD = 3%
- p<0.0001
What About Cost?

• Assumption: New technology is always more expensive
• But, look at the data!

Lumbar TDR Costs Studies

• Several studies compared TDR to fusion
  – Methods included economic modeling (Guyer et al, 2007), randomly selected patients and averaged database charges/costs (Patel et al, 2008), IDE trial patients (Leven et al, 2007), and national data registries with unmatched comparison groups (Kurtz et al, 2010)

• Although the methods used in the studies varied greatly they all found TDR was less expensive than fusion with the one exception of a cost model for ALIF with autograft only which is rarely used today

• Cost advantage vs fusion with various implants, various approaches, various graft materials with little uniformity from surgeon to surgeon
Cervical TDR
Best data, so briefly...

FDA Approved in US
• Approved
  – Prestige-ST (2007)
  – ProDisc-C (2007)
  – Bryan (2009)
  – PCM (2012)
  – SeCure-C (2012)
  – Mobi-C (1 and 2-level; 2013)
  – Prestige-LP (1-level 2014, 2-level 2016)

Current FDA Status in US
• Trial completed / withdrawn
  – Kineflex|C
• Trials ongoing
  – M6
  – Simplify (1 and 2 level studies)
• Trials ended
  – Discover
  – Neodisc
  – Cervicore
FDA IDE Trials

- All trials found TDR to be non-inferior to ACF
  - Superior on some measures
- Good results maintained for >5 yrs in studies with long-term follow-up

Mean NDI Scores for TDR and ACF in Various FDA IDE Trials showing similar results

What Happens 7-10 Years Post-TDR?
• 280 pts, 20 sites, 1 level TDR
• 265 historical control ACDF pts
  – From original Prestige study, same indications and assessments
• TDR maintained significantly improved clinical outcomes and segmental motion
• TDR at least non-inferior to ADF

<table>
<thead>
<tr>
<th>Prestige LP: 7 yr Follow-up</th>
<th>TDR</th>
<th>ACDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up rate</td>
<td>75.9%</td>
<td>70.0%</td>
</tr>
<tr>
<td>Overall success</td>
<td>74.9%</td>
<td>63.2%</td>
</tr>
<tr>
<td>NDI success</td>
<td>86.1%</td>
<td>80.1%</td>
</tr>
<tr>
<td>% satisfied</td>
<td>90.9%</td>
<td>85.6%</td>
</tr>
<tr>
<td>Re-op (index level)</td>
<td>6.4%</td>
<td>10.9%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mobi-C: 7 yr Follow-up</th>
<th>TDR</th>
<th>ACDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up rate</td>
<td>80.1%</td>
<td>73.5%</td>
</tr>
<tr>
<td>Overall success</td>
<td>55.2%</td>
<td>50.0%</td>
</tr>
<tr>
<td>NDI success</td>
<td>76.5%</td>
<td>80.8%</td>
</tr>
<tr>
<td>% satisfied</td>
<td>90.9%</td>
<td>80.8%</td>
</tr>
<tr>
<td>ASD inferior level</td>
<td>43.8%</td>
<td>63.0%</td>
</tr>
<tr>
<td>ASD superior level</td>
<td>40.4%</td>
<td>66.7%</td>
</tr>
<tr>
<td>Re-op</td>
<td>3.0%</td>
<td>12.3%</td>
</tr>
</tbody>
</table>
• 10 yr follow-up of 1 center’s FDA IDE pts
• 19 TDR, 23 ACDF (follow-up rates 84.6% and 92.0%)
• Re-op rates:
  – TDR 9%
  – ACDF 32%

In addition to pain reduction, a primary goal of TDR is to allow motion at the operated segment

Does TDR achieve this goal?

<table>
<thead>
<tr>
<th>Device</th>
<th>Pre-op</th>
<th>2 yr</th>
<th>4-5 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bryan</td>
<td>6.5°</td>
<td>8.1°</td>
<td>8.5°</td>
</tr>
<tr>
<td>Prestige</td>
<td>7.5°</td>
<td>7.6°</td>
<td>NA</td>
</tr>
<tr>
<td>ProDisc-C</td>
<td>8.5°</td>
<td>9.4°</td>
<td>8.1°</td>
</tr>
<tr>
<td>Kineflex</td>
<td>8.2°</td>
<td>9.8°</td>
<td>NA</td>
</tr>
<tr>
<td>Secure-C</td>
<td>8.5°</td>
<td>10.2°</td>
<td>NA</td>
</tr>
<tr>
<td>PCM</td>
<td>7.9°</td>
<td>5.7°</td>
<td>NA</td>
</tr>
<tr>
<td>Mobi-C</td>
<td>8.2°</td>
<td>10.6°</td>
<td>NA</td>
</tr>
</tbody>
</table>

Adjacent Segment Degeneration

- One potential benefit of cervical TDR vs. ACF is reducing the acceleration of ASD
- Literature mixed on whether this benefit has been recognized

Kineflex|C Adjacent Segment Disc Degeneration

Pre-op: no difference; Post-op: significant difference (p<0.01), indicating more patients in ACF group had greater grades of adjacent segment degeneration


Adjacent Level Subsequent Surgery Rates through 60 Months

Mobi-C FDA IDE trial data
Imaging

- One potential disadvantage of TDRs with metal components is artifact seen on MRI
- MRI technology continually improving to reduce artifact
- Materials used for TDRs is also changing that will facilitate imaging

Simplify Disc
Currently enrolling 1 and 2 level IDE study

POST-TDR Artifact on MRI
Simplify discs—lower heights match cervical anatomy

Average Disc Height From Previous IDE Study (N=525)

- Simplify Disc Coverage

Most cervical discs designed for these heights

Simplify Disc Coverage

- Elastomeric Discs
  - Elastomeric Disc
    - All Elastomer
    - CADisc
    - Mobile Bumper
    - Attached Core

Elastomeric Disc

- Bryan
- MS
- C ESP
- K2M Rhine
- Freedom

Elastic Disc

- Polymer-Bone abrasion
- Addition of HA to enhance
- Nucleus Replacement Interface problems
- Prosthetic-endplate

- Free motion between metal and polymer
- Core free to move
- Core free to rotate
- Need for surrounding envelope
- Less complex

Viscoelastic component adhered to titanium endplates, one-piece deformable but cohesive interbody spacer

- 6 degrees of freedom about 3 axes including shock absorption
- Allows limited rotation and translation with resistance to motion (elastic return property)
- Rotation center can vary freely during motion
CP ESP
Gaining wide use OUS

Freedom Disc
• Viscoelastic polyurethane
• Recently approved in Australia
• No study data
• US cervical IDE never initiated and lumbar IDE never completed

Rhine Disc - K2M
• CE Mark Jan 2016
• 1st implant Jan, 2016
• Germany, Belgium, Spin, Italy, UK, South Africa
• 300 implanted so far
  – 60% one level
  – 40% 2 level
Rhine Disc

K2M “RHINE” TDA C5-C6 ROM
Regardless of Anterior or Lateral Positioning
ROM not affected – Advantage of Viscoelastic

C5-C6 Segmental ROM (deg)
1.5Nm Flexion - 1.5 Nm Extension

K66 Foldover Load
K99 Foldover Load

K2M

Cervical total disc replacement using a novel compressible prosthesis: Results from a prospective Food and Drug Administration-regulated feasibility study with 24-month follow-up
Carl Lentzoni, MD**, Donato Caccia, MB, Thomas Donij, MD*, David Menezes, MD*, Donia D. Omran, PhD*, Hermon A. Sturess, PhD***

• 30 pts, TDR at 1 or 2 levels
• Significant improvements throughout 24 mo in:
  – NDI: 67.8 to 20.8
  – VAS neck pain: 7.7 to 2.4; right arm pain: 6.0 to 2.1; left 6.3 to 1.6
Summary

• Strong data to support lumbar and cervical TDR
• Appropriate patient selection is key
  – Indications continue to be refined
• What we are not seeing: publications, even case reports, reporting high numbers of failed TDRs, catastrophic failures, deaths from revisions, etc.
• Ongoing development of surface technology, materials, viscoelastic devices
• Patient specific design like TKA?

Summary

• Currently, greatest barrier to TDR adoption is insurance reimbursement
  – Is slowly improving
    • Cervical better than lumbar with 85% coverage vs 45% coverage
  – For lumbar, some surgeons may be slow to adopt due to need for access surgeon and/or not familiar with anterior approach
  – Also, the lumbar disc companies are not likely to jeopardize their much larger and profitable fusion business with the exception of Aesculap
Do Lumbar and Cervical TDR Have a Future?

- The most studied devices in the history of spine with Level 1 IDE data
- Strong data for lumbar and cervical TDR from variety of countries and study formats
  - 5-10+ yrfollow-up
  - Similar or superior to fusion with less ASD in longer term f/u
  - Favorable cost profile
  - No rash of reports on device failures

So there is NO QUESTION that Lumbar and Cervical TDR Are the Future!

Thank You

Center of rotation (COR) with simplify disc

Lateral Bending Pre-Op
Lateral Bending Post-Op (6 Mos)
Viscoelastic Discs

<table>
<thead>
<tr>
<th>Company</th>
<th>Cervical Devices</th>
<th>Lumbar Devices</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>AxioMed</td>
<td>Freedom Cervical</td>
<td>Freedom Lumbar</td>
<td>Features viscoelastic polymer core to mimic normal human disc characteristics</td>
</tr>
<tr>
<td>Spinal Kinetics</td>
<td>M6-C</td>
<td>M6-L</td>
<td>Features viscoelastic polymer core to simulate native disc and UHMWPE fibers to emulate native annulus</td>
</tr>
<tr>
<td>K2M Physio-L</td>
<td></td>
<td></td>
<td>Acquired Physio-L PCU disc technology from Medtronic Spine</td>
</tr>
</tbody>
</table>

Appropriately Selected Patients

- LBP +/- leg pain of lesser severity
- Failed >6 mo non-op care (PT, meds, education, activity modification, etc.)
- MRI and disco correlative with symptoms and physical exam
  - DDD at 1-2 levels
  - No other spine pathology
- No significant psychological problems
- Good bone quality

Adjacent Segment Disease, Natural History or Biomechanical??

Literature Review

- Biomechanically fusions increase intradiscal pressure, facet loading, and hypermobility above and beyond natural history
- Radiographic 5.2%-100% at 36-360 mo f/u
- Symptomatic 5.2-18.5% at 44.8-164 mo f/u (higher with pedicle screws, 12.2-18.5%)
- Risk factors = pedicle screws, facet joint violation, sagittal malalignment, and fusion length

Park et al., Spine 2004
Mean NDI Scores for TDR and ACF in Various FDA IDE Trials

- As seen in the graph, data is extremely reproducible across multiple devices
  - All represent multicenter trials
  - Most conducted at different centers
  - Supports generalizability of outcomes

Charité 10-13 Year Follow-up

- Old evaluation methods, but excellent follow up of >90% with 90% “exe-gd”

CP ESP

- Titanium endplates and hydroxyapatite coating
- Inner and outer core (polycarbonate urethane)
- 6 degrees of freedom restores “natural” mobility
Inferior and Superior ASD at 60 mos in 2-level Study (Kellgren-Lawrence Scale)

**Bryan: 10 yr Follow-up**

Mean NDI Scores

Mean VAS Scores

**Quality of Motion Study**

Experimental protocol:
- Intact
- C5-C6 TDA Anterior placement
- C5-C6 TDA Optimal placement
- C6-C7 TDA Optimal placement
- C5-C6 TDA Lateral placement

Cervical spine set-up showing intact specimen.
The human disc provides:
- Shock absorption
- Stability
- Controlled motion

Elastomeric Polymers:
- Motion occurs within polymer
- Provides shock absorption
- Mimics properties of natural disc
- Attractive & intuitive solution to surgeons

Elastomeric Designs
- Ball & Socket Design: Inherently UNSTABLE
- Elastomeric Design: Inherently STABLE

From Other Countries
- Often relatively small numbers of pts
- Good results for cervical TDR, no indication of less favorable outcomes compared with ACF

From other Countries, Mobi-C® and Anterior Cervical Discectomy and Fusion using the Solis® Cage
- 332 cases; 64% follow-up at 5 yrs
- Significantly improved scores for: neck pain, arm pain, EQ5-D
  - Significantly reduced analgesic use
- 4.5% revision surgery

Europ Spine J 22(8):1723-1730, 2013
Meta-analysis: TDR vs. ACF

- No significant differences in NDI, SF-36, or pain scores
- TDR had significantly:
  - Lower re-op rate
  - Greater neurological success rate
  - Lower re-op rate for adjacent-level when analyzed using fixed effects model, but not significant using random effects model

Upadhyaya et al., J Neurosurg Spine, 2012

What about the Cost of Cervical TDR?

- Used outcome literature, NIS, and Medicare reimbursement data to create decision tree model for cost-effectiveness analysis
- Cost model designed for period of 20 yrs
- TDR was more beneficial and less expensive than ACF
Cost

Single-level cervical radiculopathy: clinical outcome and cost-effectiveness of four techniques of anterior cervical disectomy and fusion and disc arthroplasty

Cost

Other cost studies also favor TDR

Only construct less expensive than TDR was Brantigan cage w/o graft - not standard of care

TDR less expensive than ACF

Total Costs: TDR ~ 12% Lower

<table>
<thead>
<tr>
<th></th>
<th>TDR</th>
<th>ACF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index event</td>
<td>$20,722</td>
<td>$22,379</td>
</tr>
<tr>
<td>Index event + 90</td>
<td>$22,761</td>
<td>$25,029</td>
</tr>
<tr>
<td>post-op period</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge to 6</td>
<td>$791</td>
<td>$1,236</td>
</tr>
<tr>
<td>weks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 weks to 3</td>
<td>$1,216</td>
<td>$1,497</td>
</tr>
<tr>
<td>max</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 to 12 min</td>
<td>$4,127</td>
<td>$4,566</td>
</tr>
<tr>
<td>13 to 18 min</td>
<td>$3,106</td>
<td>$3,594</td>
</tr>
<tr>
<td>18 to 24 min</td>
<td>$2,862</td>
<td>$3,596</td>
</tr>
<tr>
<td>24 to 36 min</td>
<td>$3,753</td>
<td>$4,806</td>
</tr>
<tr>
<td>36 to 48 min</td>
<td>$4,689</td>
<td>$5,128</td>
</tr>
<tr>
<td>TOTAL</td>
<td>$34,979</td>
<td>$39,820</td>
</tr>
</tbody>
</table>

Radcliff et al., Spine 2015

Insurance industry data generally unavailable

Blue Health spun off as a for-profit venture by "the Blues", allowing access to payment database

Allowed authors to "work backwards" from payments to clinical events (post-op, peri-op, and pre-op) by CPT and ICD-9 codes

Safety and cost-effectiveness of outpatient cervical disc arthroplasty
Single level IDE study – VAS (Neck and Arm)

Mobi-C: Adjacent Segment Degeneration (Kellgren-Lawrence Scale)

Mobi-C: 7 yr Follow-up

- Improvement in NDI, VAS neck pain, and SF-12 scores similar between groups
- TDR group maintained segmental ROM at every time point through 84 mo
- No significant difference in rates of AEs or major complications

* Adjacent segment degeneration significant (p<0.05)