Barricaid® Anular Closure Device

December 12, 2017

Intrinsic Therapeutics, Inc. (P160050)

Orthopaedic and Rehabilitation Devices Panel

Introduction

Cary Hagan

President and CEO

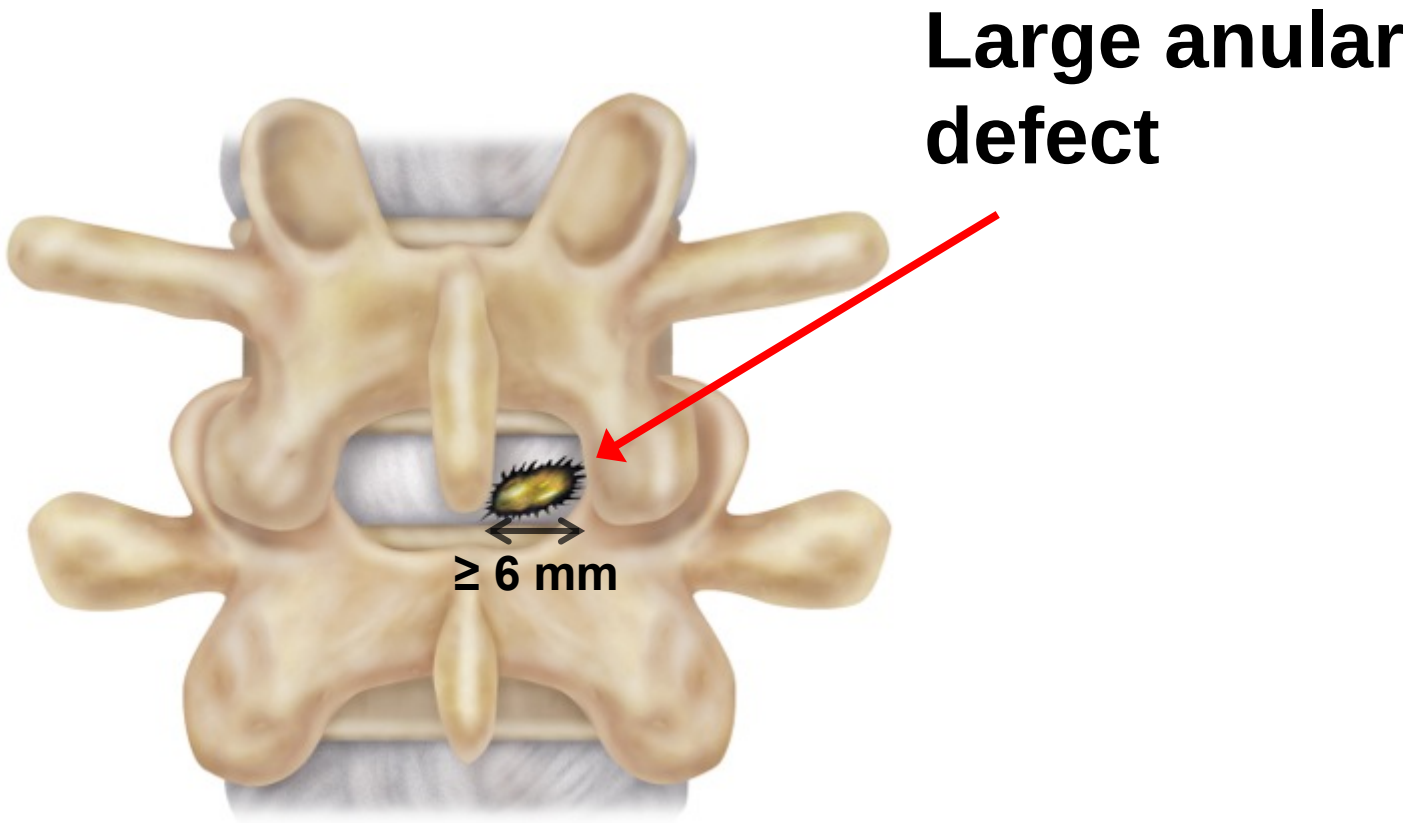
Intrinsic Therapeutics, Inc.

Focused on Solving Challenge of Reherniation After Discectomy

- Discectomy is safe and effective procedure to treat herniated lumbar disc
- Subset of patients have high risk of reherniation and reoperation

Defined Patient Population: Large Anular Defects Following Discectomy

- High risk of reherniation and reoperation



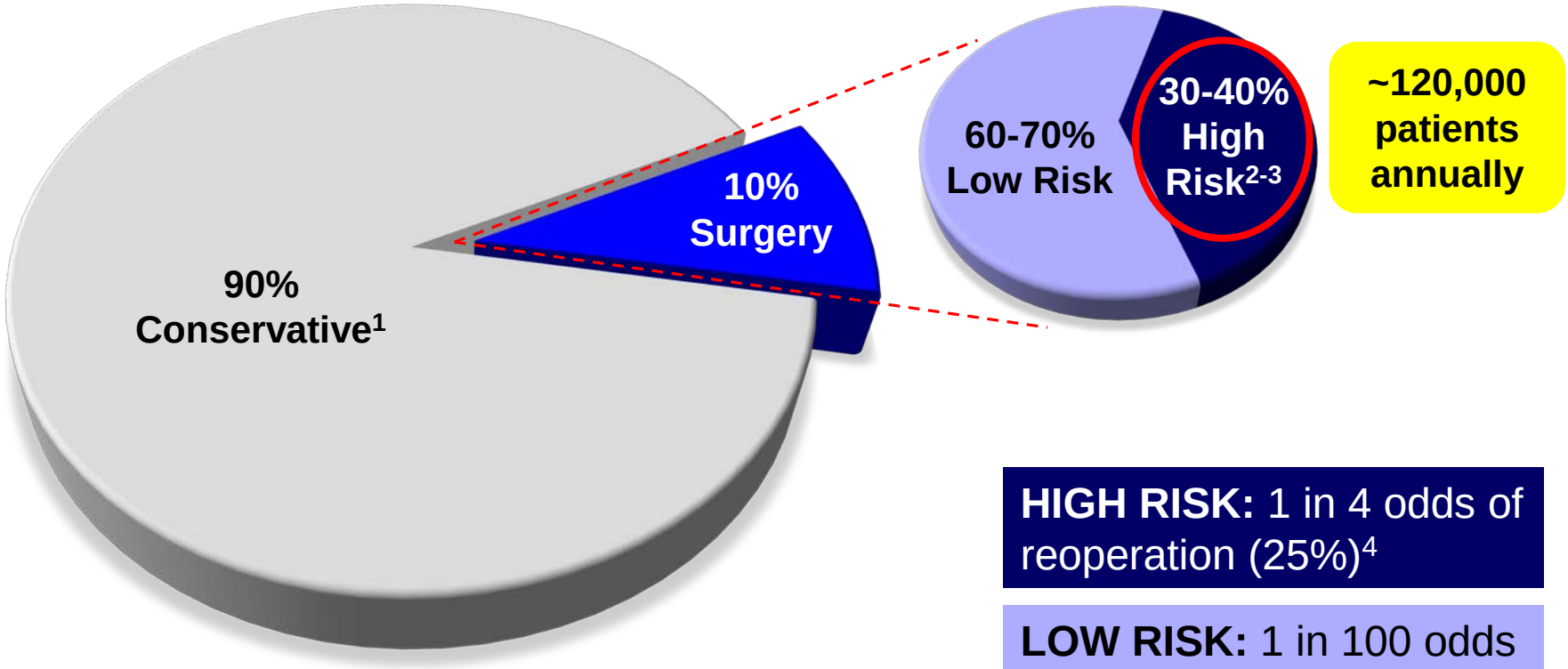
Presentation Objectives

- Demonstrate quality of trial design
  - Most comprehensive trial to date for lumbar discectomy
- Prove safety, effectiveness and positive benefit/risk in this high-risk patient population
- Address radiographic observations

Sciatica, Disc Herniation, Discectomy

US SCIATICA PATIENTS
3–4M Annually

US DISCECTOMY PATIENTS
300–400K Annually



HIGH RISK: 1 in 4 odds of reoperation (25%)[4]

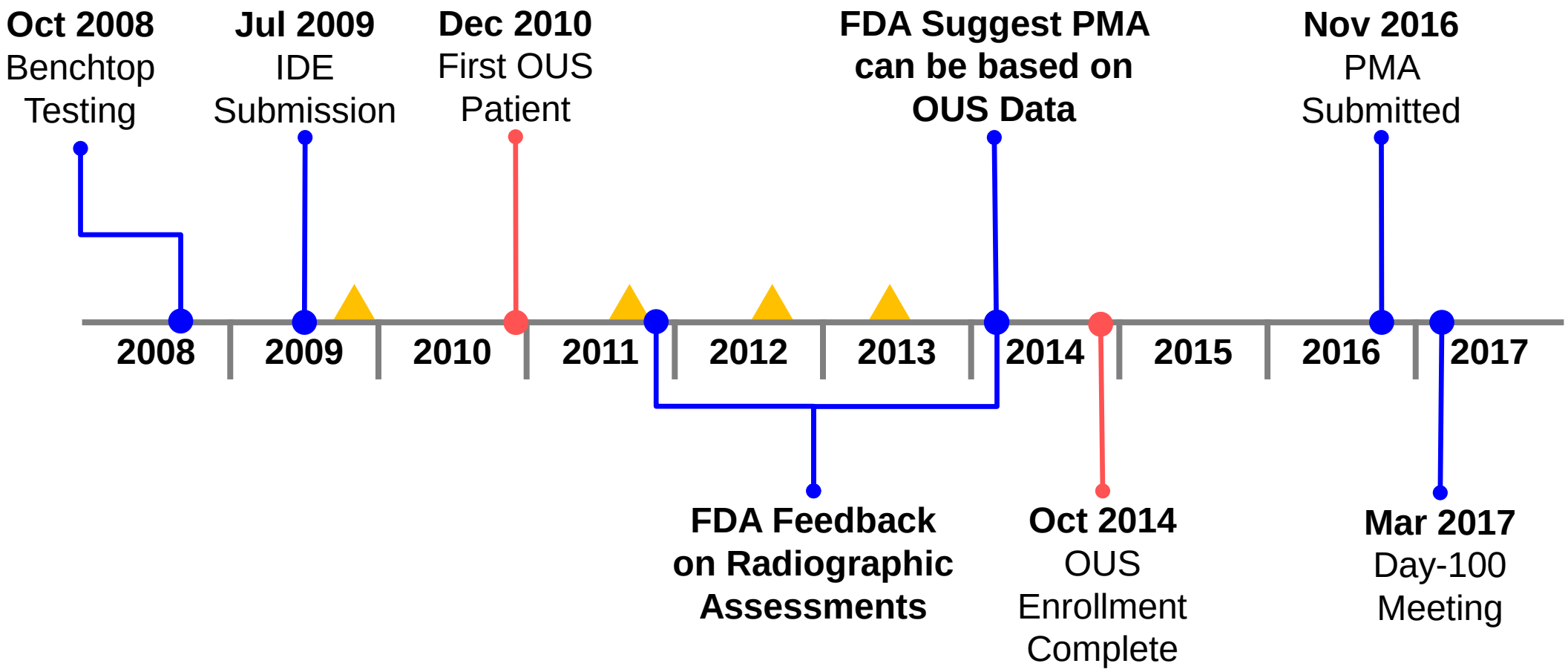
LOW RISK: 1 in 100 odds of reoperation (1.1%)[4]

1. Gibson (2007); 2. Miller (2017) 3. Wera (2008); 4. Carragee (2003)

Device Background

- Blocks large anular defects with flexible occlusion component
  - Maintains discectomy benefits
  - Reduces reherniations and additional surgeries
- CE Marked since 2009
  - ~6,000 cases worldwide
  - > 20 countries

Regulatory History



▲ FDA feedback on Study Design

Agenda

Clinical Need / Study Design	**Raymond Golish, MD, PhD** Chief of Surgery Jupiter Medical Center
Safety and Effectiveness / Long-Term Results	**Gerrit J. Bouma, MD** Chief of Neurosurgery OLVG Hospital Amsterdam, the Netherlands
Endplate Change Observations & Evaluation	**Adisa Kuršumović, MD** Neuro and Vascular Surgery Donauisar Klinikum Deggendorf, Germany
Benefit-Risk	**Matthew McGirt, MD** Associate Professor University of North Carolina
Moderator	**Glenn Stiegman, MS** Musculoskeletal Clinical Regulatory Advisors (MCRA)

Additional Experts

- **Scott Berry, PhD**
  Bayesian Statistical Consultant
  President, Senior Statistical Scientist
  Berry Consultants, LLC

- **Ravi Kamath, MD**
  DSMB Member
  Radiologist
  Fairfax Radiological Consultants

- **David Kim, MD**
  DSMB Chairman
  Orthopedic Surgeon
  New England Baptist Hospital

- **Peggy Lalor, PhD**
  Histopathologist
  President and CEO
  Histion, LLC

- **Greg Maislin, MS, MA**
  Study Statistician
  Principal
  Biomedical Statistical Consulting

- **Mark Schweitzer, MD**
  Radiologist / EPC Consultant
  Chairman, Professor
  Department of Radiology
  School of Medicine, Stony Brook University

- **Ryan Siskey, MS**
  Explant and Mechanical Testing Analyst
  Principal
  Exponent

- **Oscar Yeh, PhD**
  Vice President, Research
  Intrinsic Therapeutics, Inc.

Unmet Need

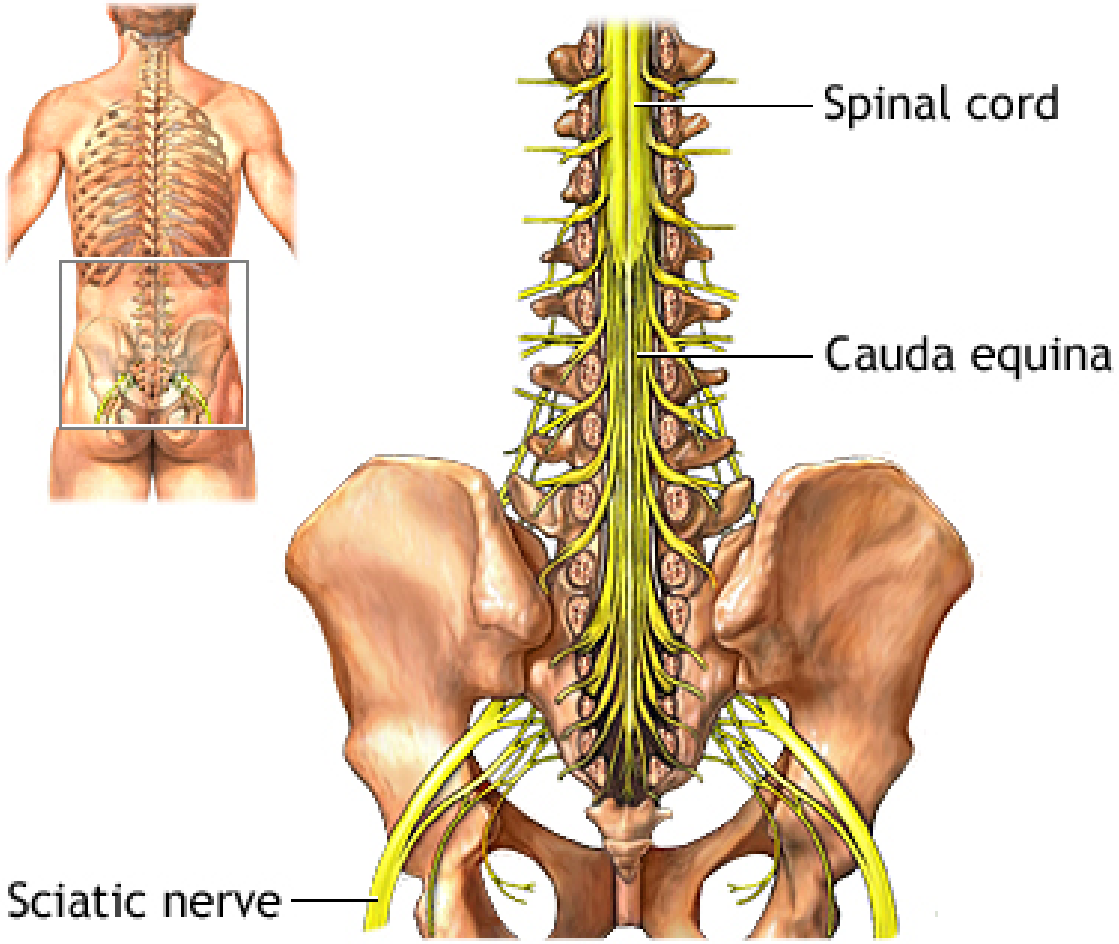
S. Raymond Golish, MD PhD MBA

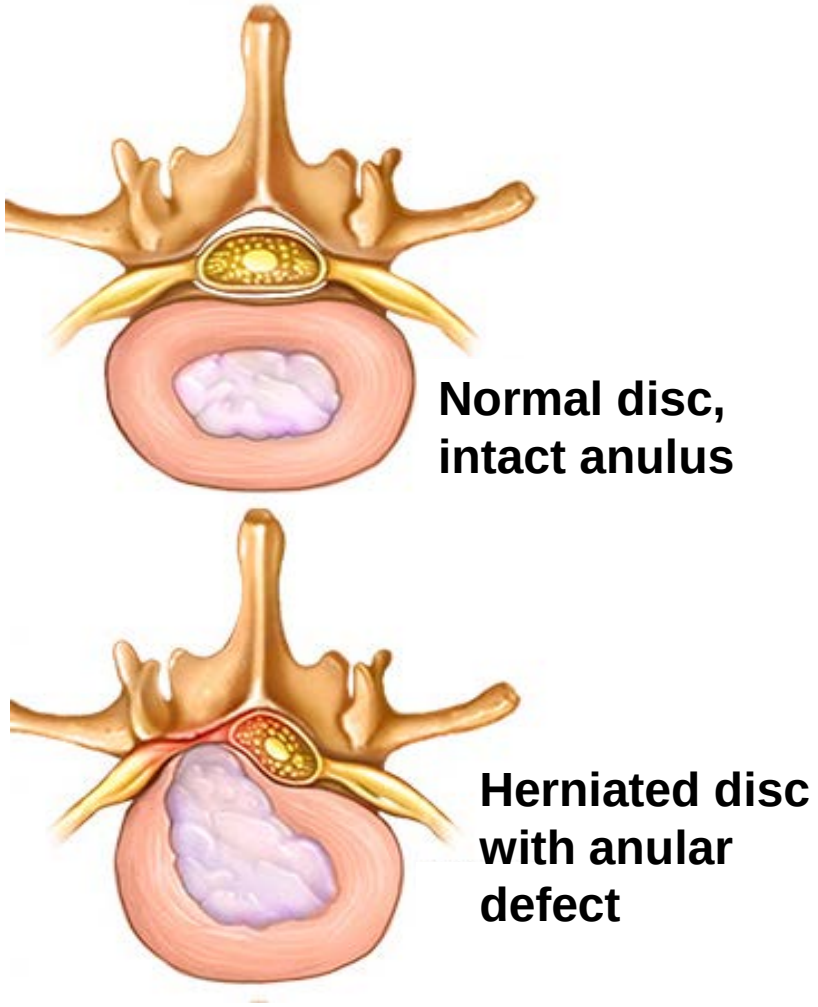
Chief of Surgery and Chief Quality Officer

Jupiter Medical Center

Palm Beach, FL

Herniated Lumbar Disc: Anatomy





Normal disc, intact anulus

Herniated disc with anular defect

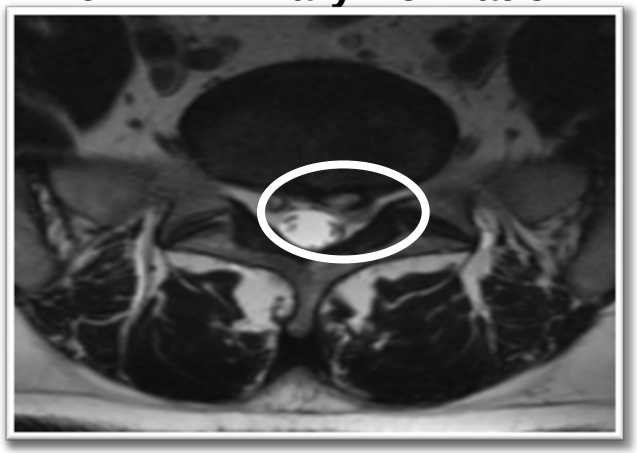
Illustration sources: Mayo Foundation for Education and Research, MedlinePlus.gov

Herniated Lumbar Disc: Discectomy

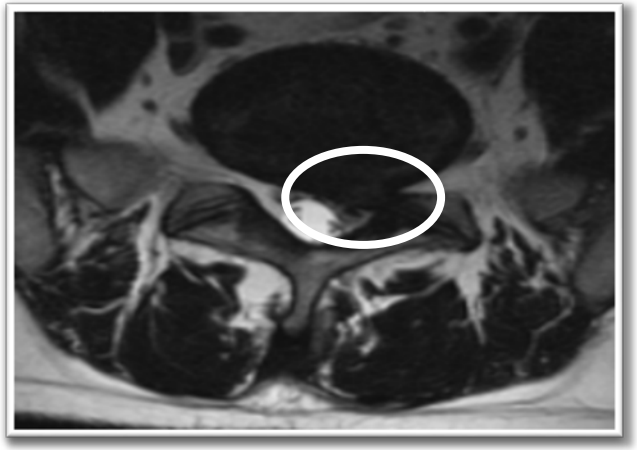
- Well done microsurgical discectomy is a great operation
- Microsurgical discectomy is not perfect
- Recurrent herniated disc after surgery is a recognized problem

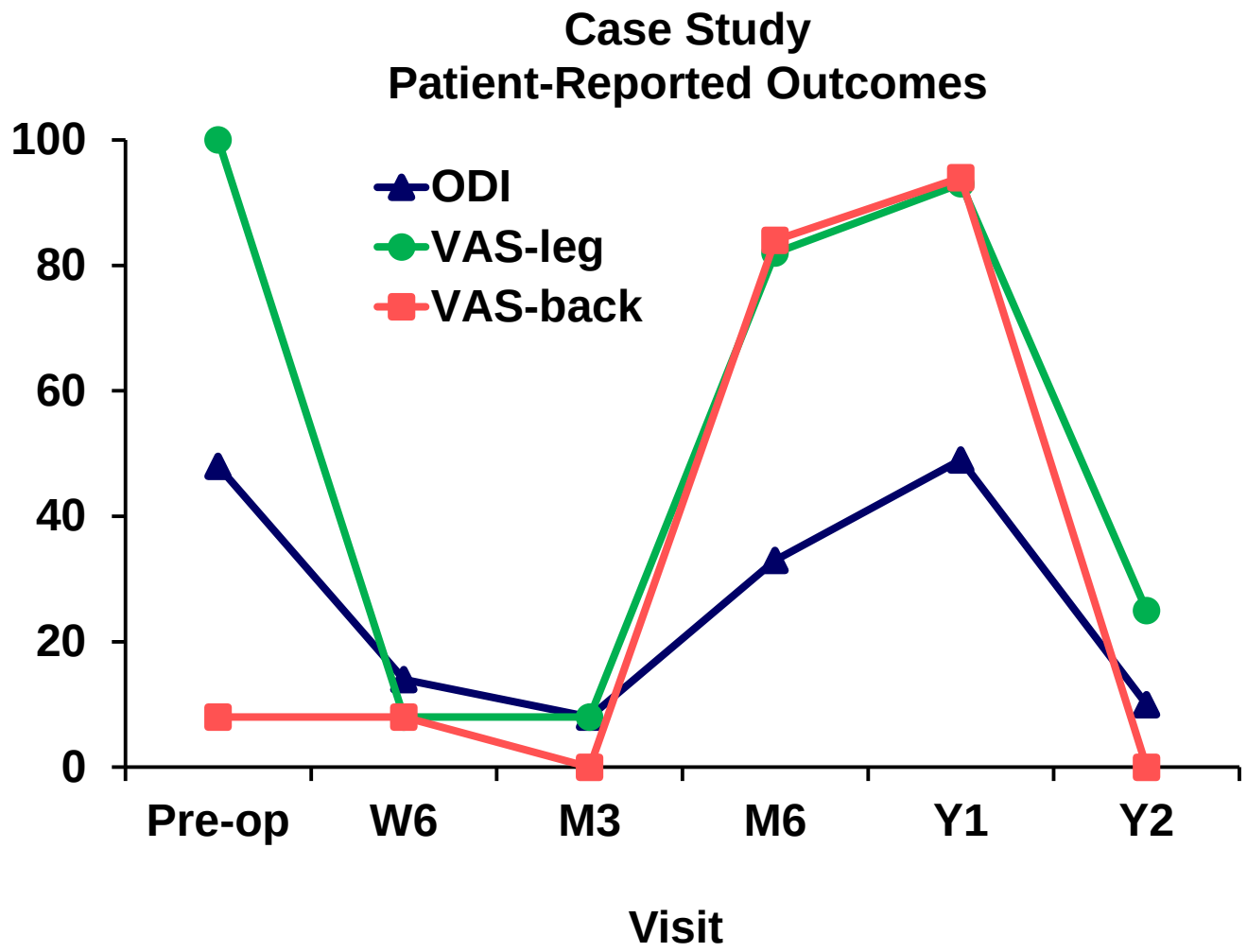
Recurrent Herniation

2012 – Primary Herniation



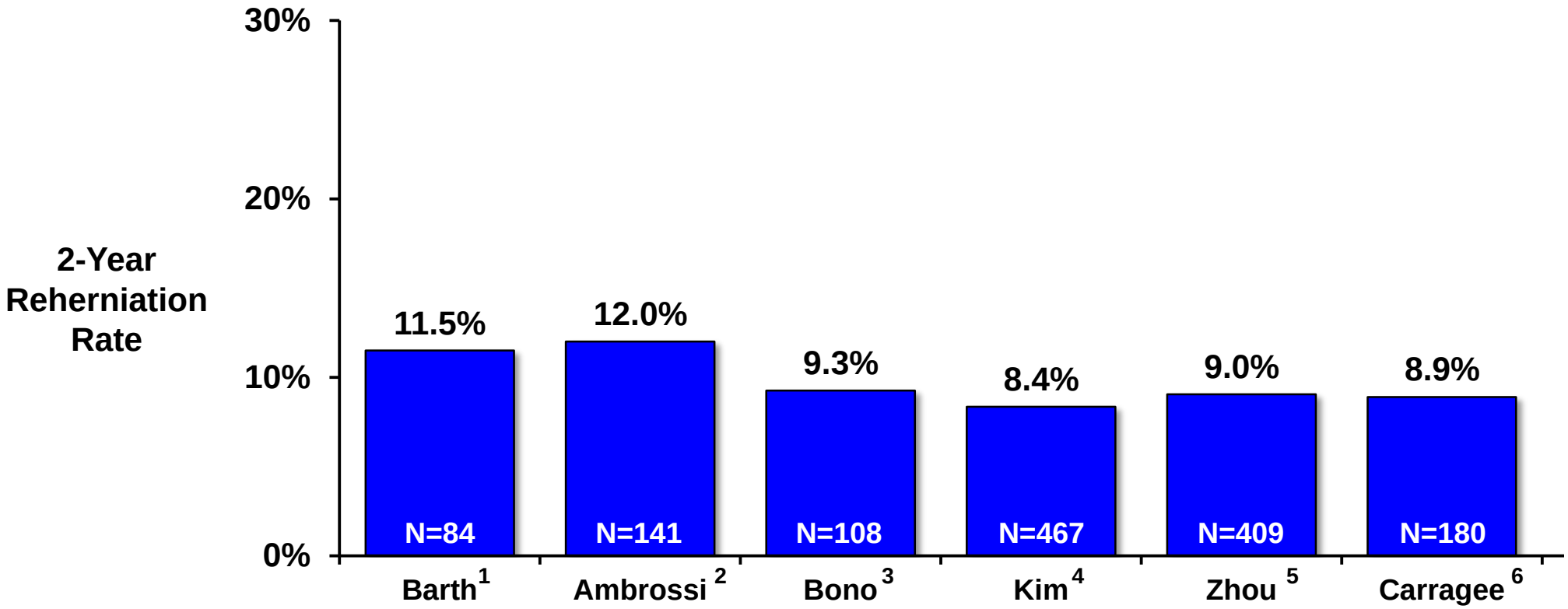
2013 – Reherniation





43 y/o Caucasian; BMI 23.54
Left sided control discectomy; L5-S1 level on 5/14/2012 (index SX)

Reherniation: General Population



"All Comers" Discectomy Population: 8-12% Reherniation Rate

1. Barth (2008); 2. Ambrossi (2009); 3. Bono (2017); 4. Kim (2015); 5. Zhou (2016); 6. Carragee (2003)

Defined High Risk Population

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3–4M Annually

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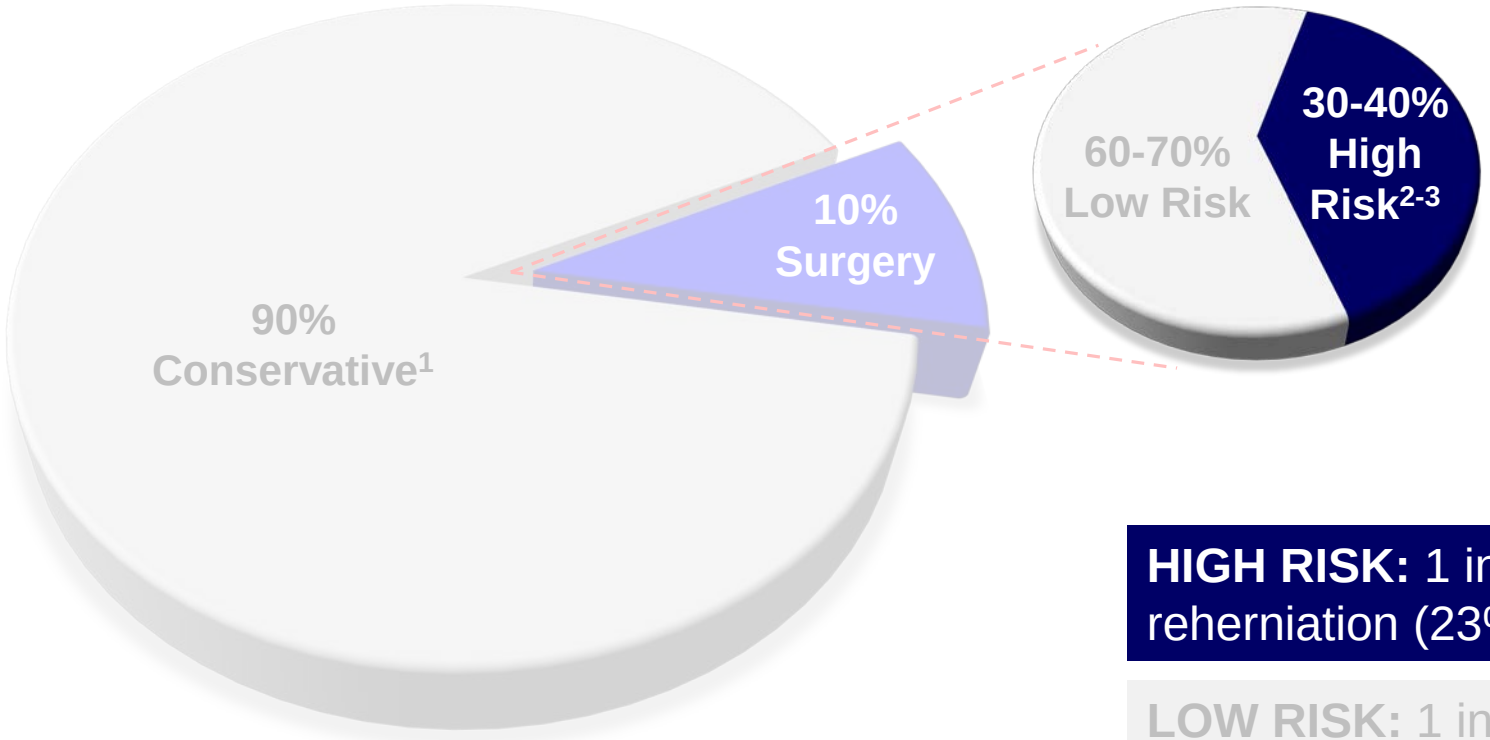
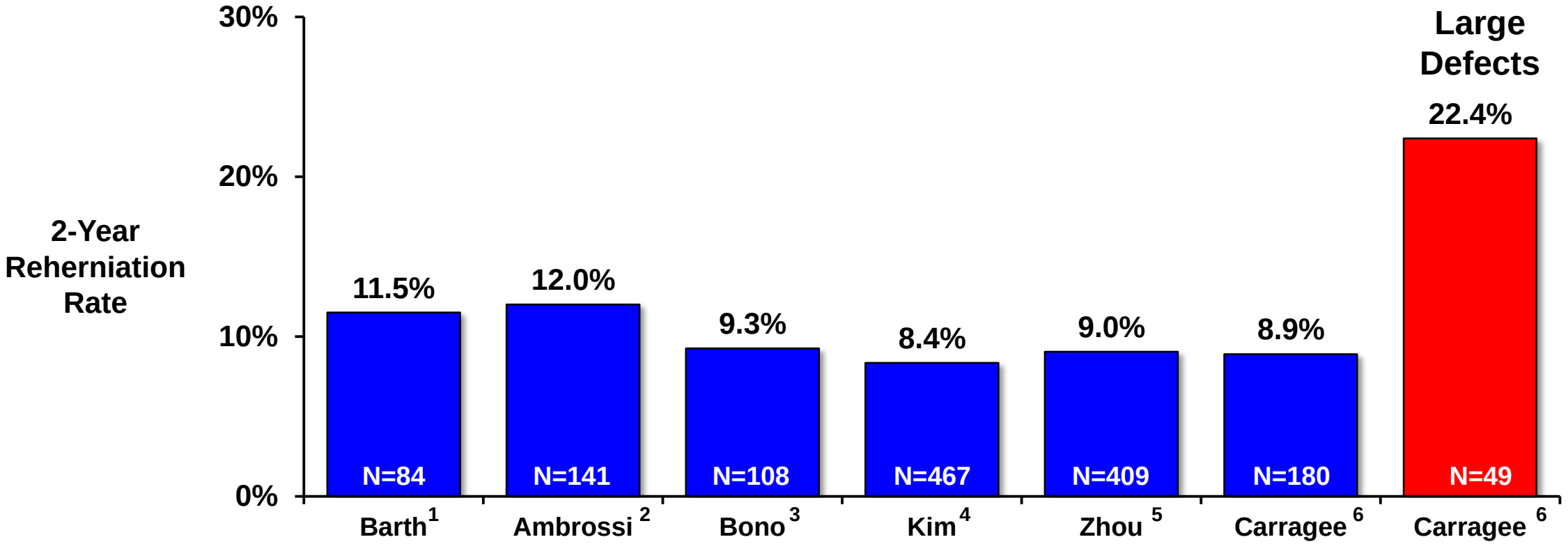


HIGH RISK: 1 in 4 odds of reherniation (23%)[4]

LOW RISK: 1 in 100 odds of reherniation (1.1%)[4]

1. Gibson (2007); 2. Miller (2017) 3. Wera (2008); 4. Carragee (2003)

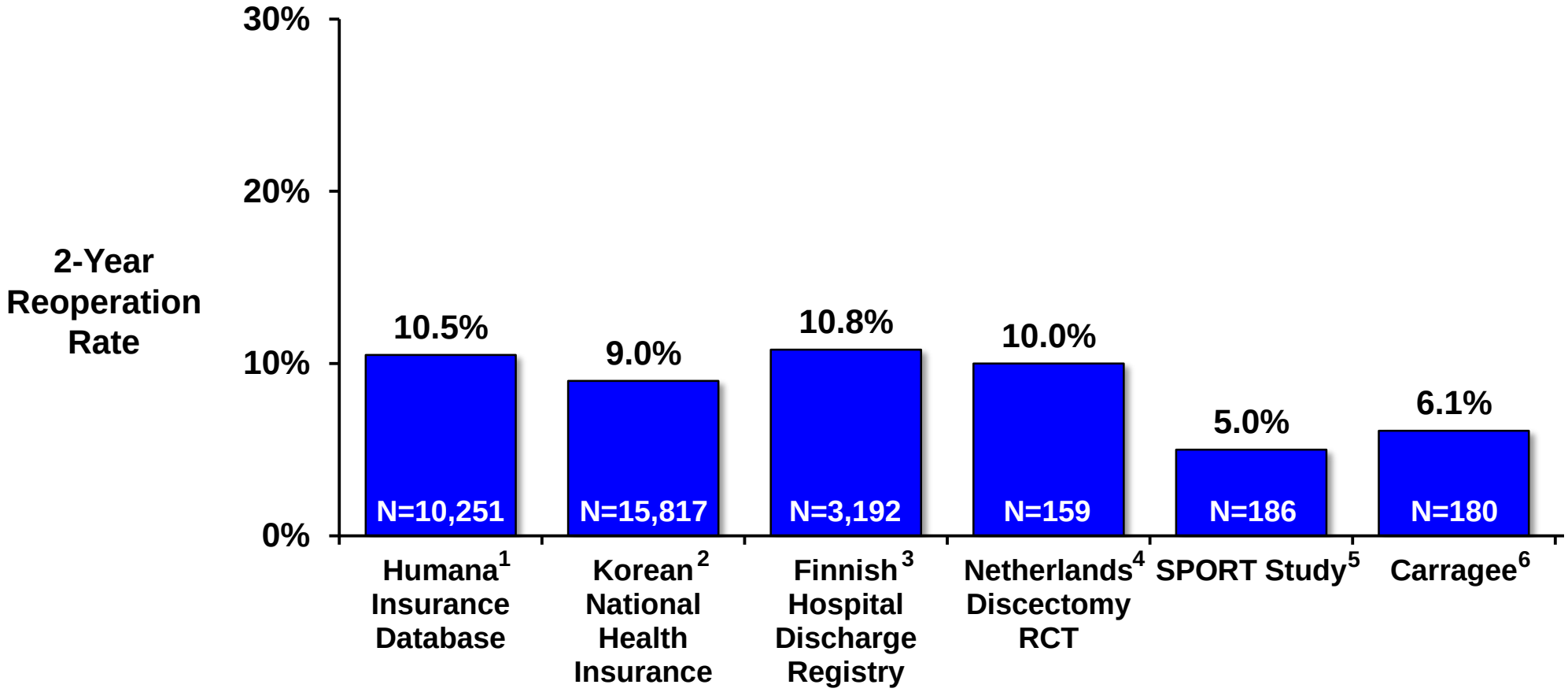
Reherniation: High-Risk Group



Large Anular Defects = Higher Recurrence Rate
Meta-Analysis: Odds Ratio = 2.5 (p=0.004)[7]

1. Barth (2008); 2. Ambrossi (2009); 3. Bono (2017); 4. Kim (2015); 5. Zhou (2016); 6. Carragee (2003); 7. Miller (2017)

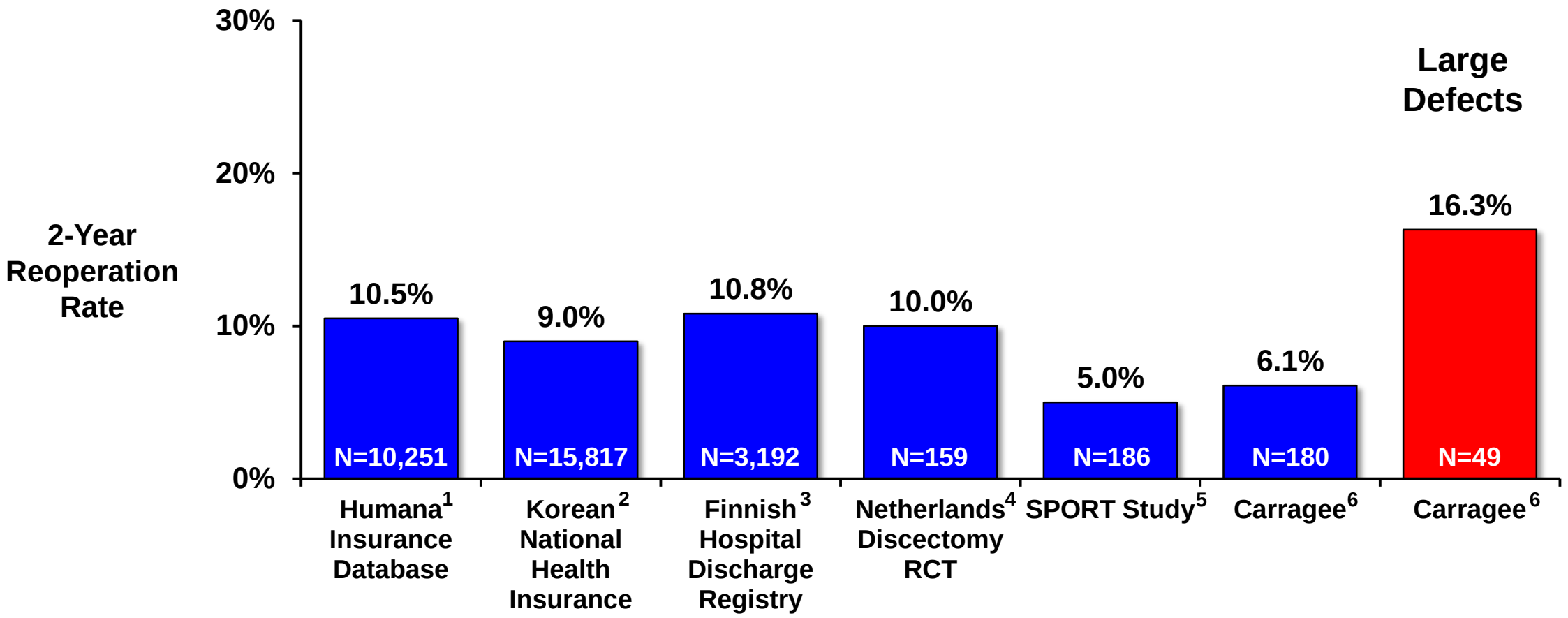
Reoperation: General Population



"All Comers" Discectomy Population: 5-11% Reoperations at 2 Years

1. Heindel (2017); 2. Kim (2017); 3. Keskimaki (2000); 4. Arts (2011); 5. Weinstein (2006); 6. Carragee (2003)

Reoperation: High-Risk Group



Large Anular Defects = Higher Recurrence Rate, Meta-Analysis: Odds Ratio = 2.3 (p<0.001)[7]

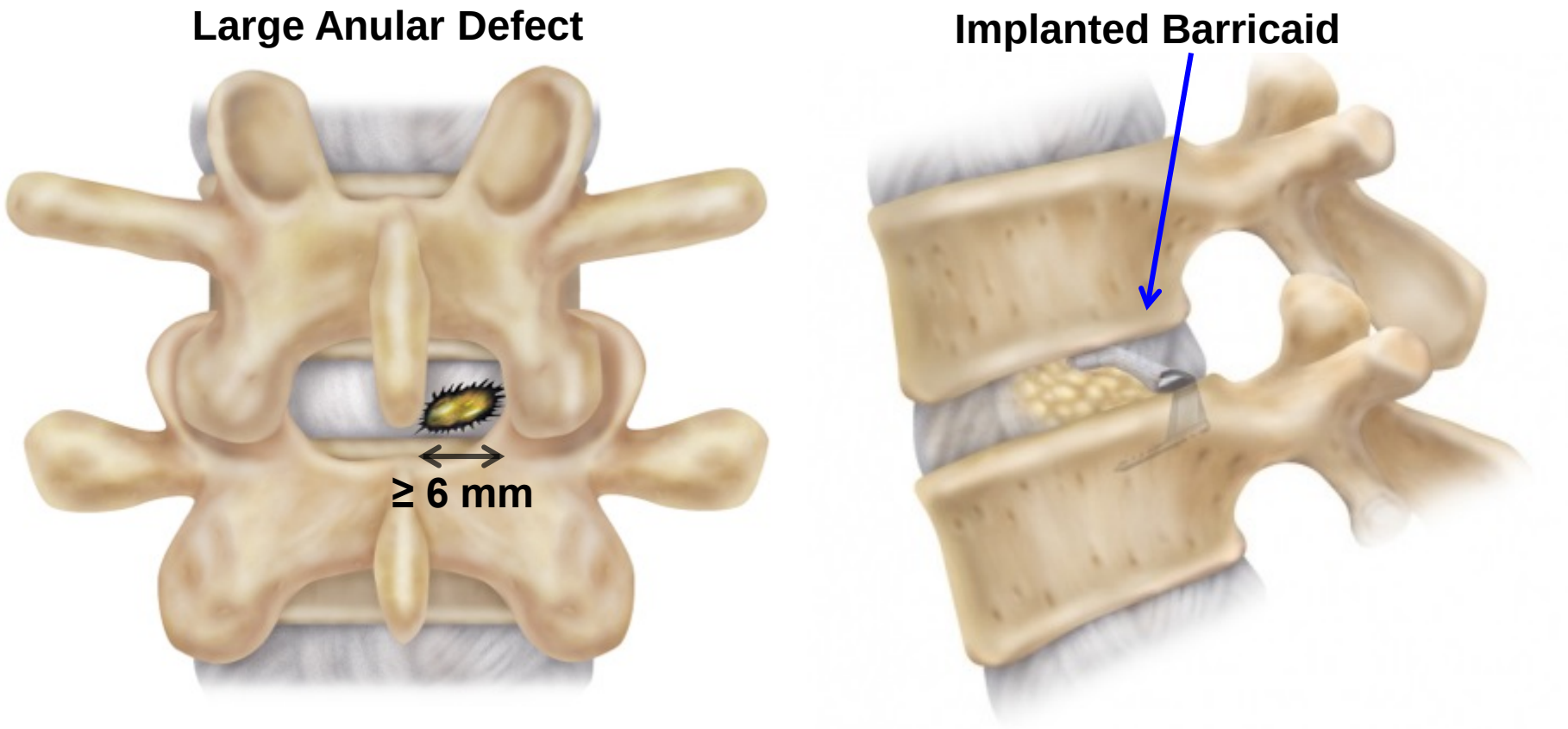
1. Heindel (2017); 2. Kim (2017); 3. Keskimaki (2000); 4. Arts (2011); 5. Weinstein (2006); 6. Carragee (2003); 7. Miller (2017)

Reoperation Leads to Chronic Disability

- Patient prognosis poor 2+ years following reoperated reherniation, with significantly:
  - Worse function (ODI)[1]
  - Less satisfaction with outcome[1]
  - More using opioids[2] and at higher doses[3]
  - Lower rate of return to work[2]

1. Leven (2015); 2. O'Donnell (2017); 3. Ahn (2015)

Barricaid Device Blocks Large Anular Defects Following Discectomy



Barricaid Intended to Reduce Risk of Reherniation and Reoperation

Barricaid Anular Closure Device

Occlusion Component

- Woven, flexible, non-biodegrading
- Dacron
- Platinum iridium marker

Titanium Anchor

- Textured surface for fixation
- Titanium alloy (Ti-6Al-4V ELI)

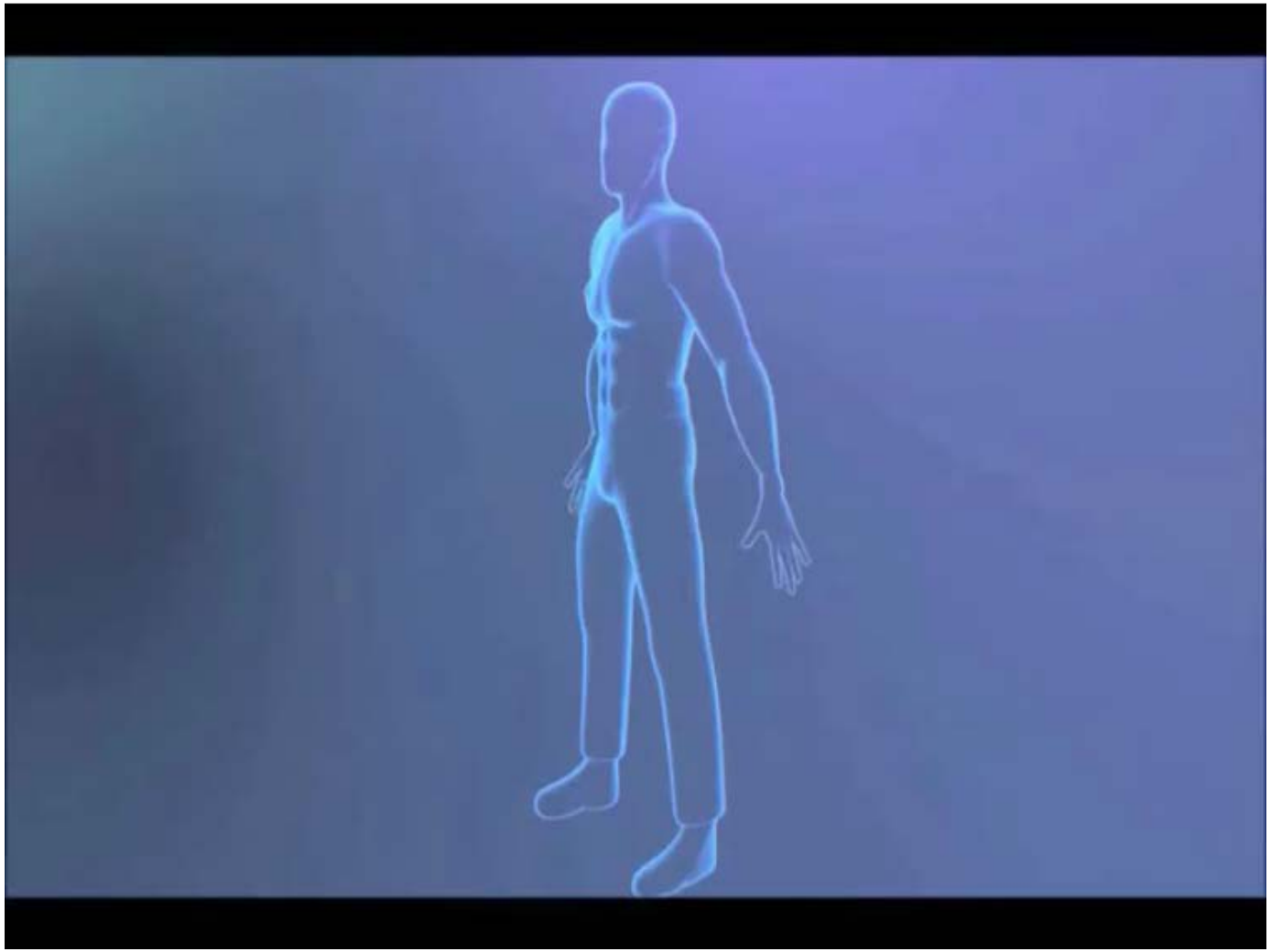
Barricaid Delivery Tool and Device Sizes

Pre-Market Safety Assessment

- Mechanical failure testing
- 6 month small mammal study demonstrated lack of neurotoxicity
- 12 month primate study established device integrity
  - Marked device size mismatch with baboon spine impacts findings
  - No fractures or migrations
  - No systemic toxicity
  - Inflammation only evident after endplate was disrupted
  - Similar findings in control group
- Cadaver implantation - validated surgical technique
- Pilot clinical study established initial safety profile

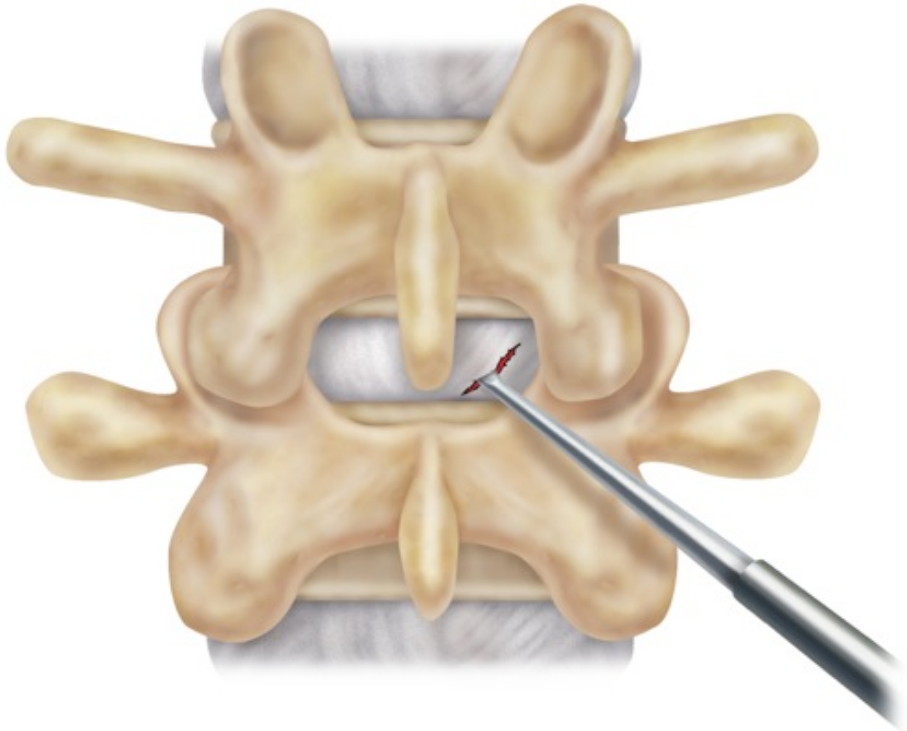
Exhaustive Safety Assessment Demonstrated Reasonable Assurance of Safety

Barricaid Implantation Technique

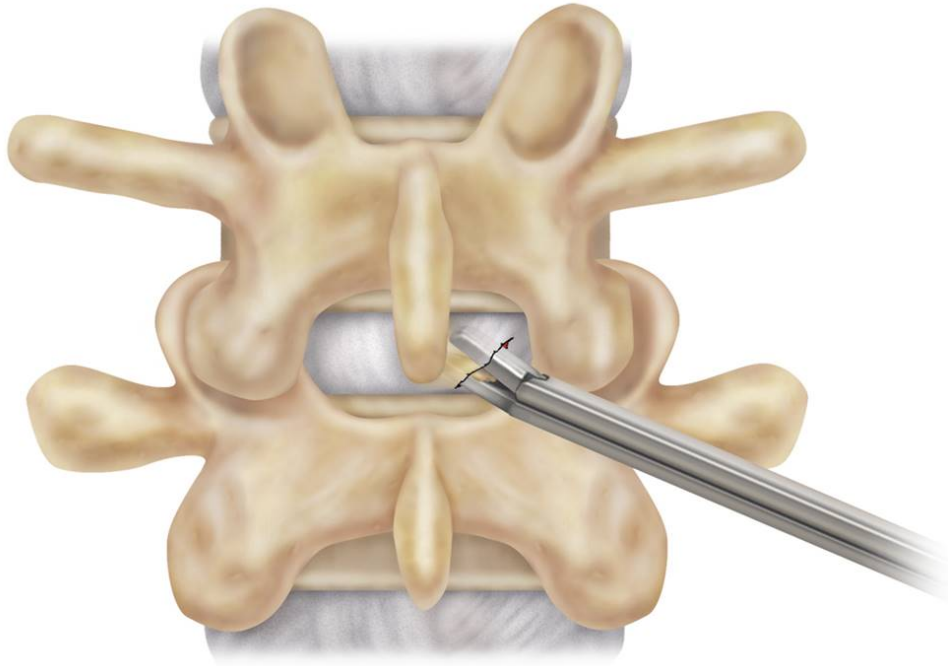


Discectomy Technique

Identification of defect



Minimal removal of nucleus (loose/free fragments)



Proposed Indication

The Barricaid is indicated for patients with radiculopathy (with or without back pain), a posterior or posterolateral herniation, characterized by imaging confirmation of neural compression using MRI, and a large anular defect (e.g., between 4–6 mm tall and between 6–12 mm wide) post discectomy, at one level between L4 and S1.

Barricaid Addresses Unmet Need in High-Risk Population

- Patients with ≥ 6 mm width defects are at significantly higher risk of reherniation and reoperation[1]
  - Study enrolled only this population
- Study patients treated with surgical standard of care
  - Limited discectomy
  - Modern and standard microsurgery technique

1. Miller (2017)

Study Design

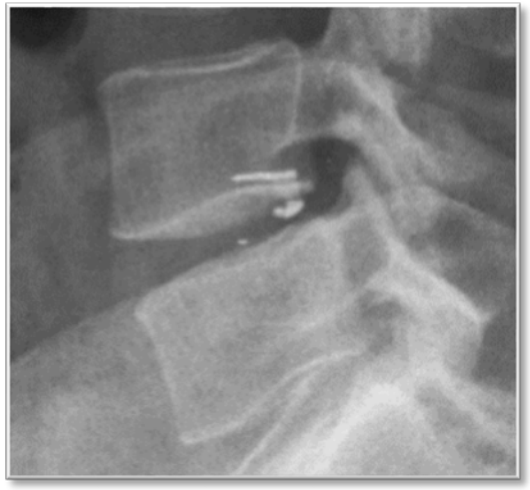
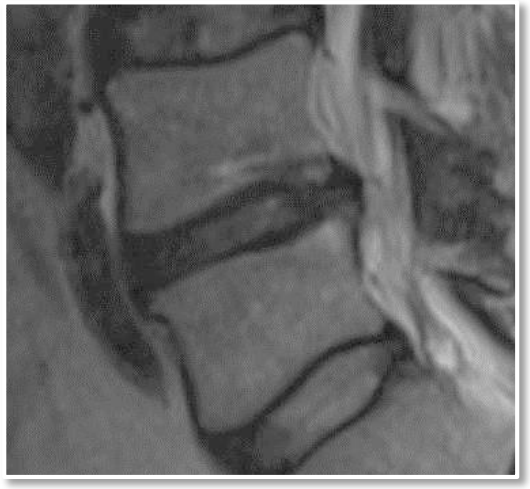
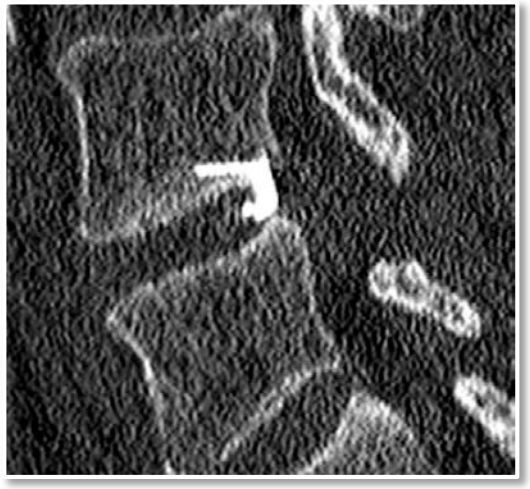
Barricaid Pivotal Trial

- Multi-center, two-arm, randomized, controlled trial
- Randomized 1:1 intra-operatively
  - Discectomy (surgical standard) with and without Barricaid
- Superiority at 2 years, defined prospectively
- Co-primary endpoints:
  - Reherniations
  - Composite: Pain, function, safety, effectiveness

Follow-up Protocol

Visit	Assessments
Pre-op	▪ History and neurological exam ▪ PROs: ODI, VAS, SF-36 ▪ X-rays, MRI, CT
Surgery	▪ Defect and nucleus removed, measured, recorded ▪ 1:1 web-based randomization ▪ Skin closure or implantation of Barricaid
Week 6 **Month 3** **Month 6**	▪ Neurological exam ▪ PROs: ODI, VAS, SF-36 ▪ X-rays
Annual Follow-up through 5 Years	▪ Neurological exam ▪ PROs: ODI, VAS, SF-36 ▪ X-rays, MRI, CT

Extensive Imaging Evaluation Protocol

Plain Radiographs (every timepoint)	**MRI** (annually)	**CT** (annually)
		

Longitudinal Imaging in Three Modalities

Reherniation: MRI Assessments

Every scheduled and unscheduled MR reviewed by core lab:	
Presence	None, protrusion, extrusion, sequestration
Side	Ipsilateral, midline, contralateral
Location	Paramedial, foraminal, extra-foraminal
Extent	Radial from disc (mm)
Breadth	≤ 25% vs > 25% of entire disc circumference

Key Inclusion Criteria

- Age 21 to 75 years old
- Anular defect 4–6 mm tall and 6–10 mm wide
- Minimum posterior disc height of 5 mm
- ≥ 6 weeks of failed conservative treatment
- Posterior or posterolateral disc herniation at one level between L1–S1 (MRI)
- Visual Analog Scale (VAS) leg pain ≥ 40/100 mm
- Oswestry Disability Index (ODI) ≥ 40/100
- Radiculopathy including positive provocative signs

Key Exclusion Criteria

- Prior surgery at index level
- Spondylolisthesis > Grade I
- Scoliosis > 10° (angular and rotational)
- BMI > 40 kg/m^2
- Bone quality screening (SCORE questionnaire)
  - DEXA T-Score < -2.0, if required by SCORE

Independent Third Party Evaluation and Oversight

- Medical Ethics Committee (EC) approval and oversight
- Histopathology and explant analysis
- Radiographic core lab
  - 2 US board-certified radiologists assess each image
  - Third available for adjudication
- Data Safety Monitoring Board (DSMB)
  - 3 US board-certified spine surgeons
  - 1 US board-certified radiologist
  - Oversaw study safety, enforced stopping rules
  - Adjudicated all AEs

Two Co-Primary Endpoints Assessed at 24 Months

Primary Endpoint	Definition of Success
Reherniation	No evidence of recurrent herniation at index level at any time up to and including 24-month follow-up, regardless of symptoms, confirmed radiographically or surgically.
Safety and Effectiveness Composite (8 components)	▪ 20 mm improvement in VAS Leg ▪ 15-point improvement in ODI ▪ No deterioration of neurological status at index level ▪ No spontaneous fusion ▪ Maintenance of average disc height ≥ 75% compared to preoperative ▪ No reherniation at index level (on either side, confirmed radiographically or surgically) ▪ No secondary surgical interventions (SSI) ▪ No implant migration or loss of device integrity (confirmed radiographically)

Establishing Superior Safety and Effectiveness

Grouping	Composite Component	Success Criteria	Between-Cohorts Expectation	Per-Patient Required for Composite
Discectomy-specific Safety and Effectiveness	VAS Leg	> 20 mm improvement	Similar	✓
	ODI	> 15 pt improvement		✓
	Neuro	Maintenance or improvement		✓
General Radiographic Outcomes	Spontaneous Fusion	None at index level	Similar	✓
	Disc Height	Maintain > 75%		✓
Barricaid-specific Safety and Effectiveness	Reherniation	No reherniations	Superior	✓
	SSI	No SSIs		✓
	Device Integrity	No integrity observations		✓

Primary Effectiveness and Safety Results

Gerrit J. Bouma, MD

Head, Department of Neurosurgery

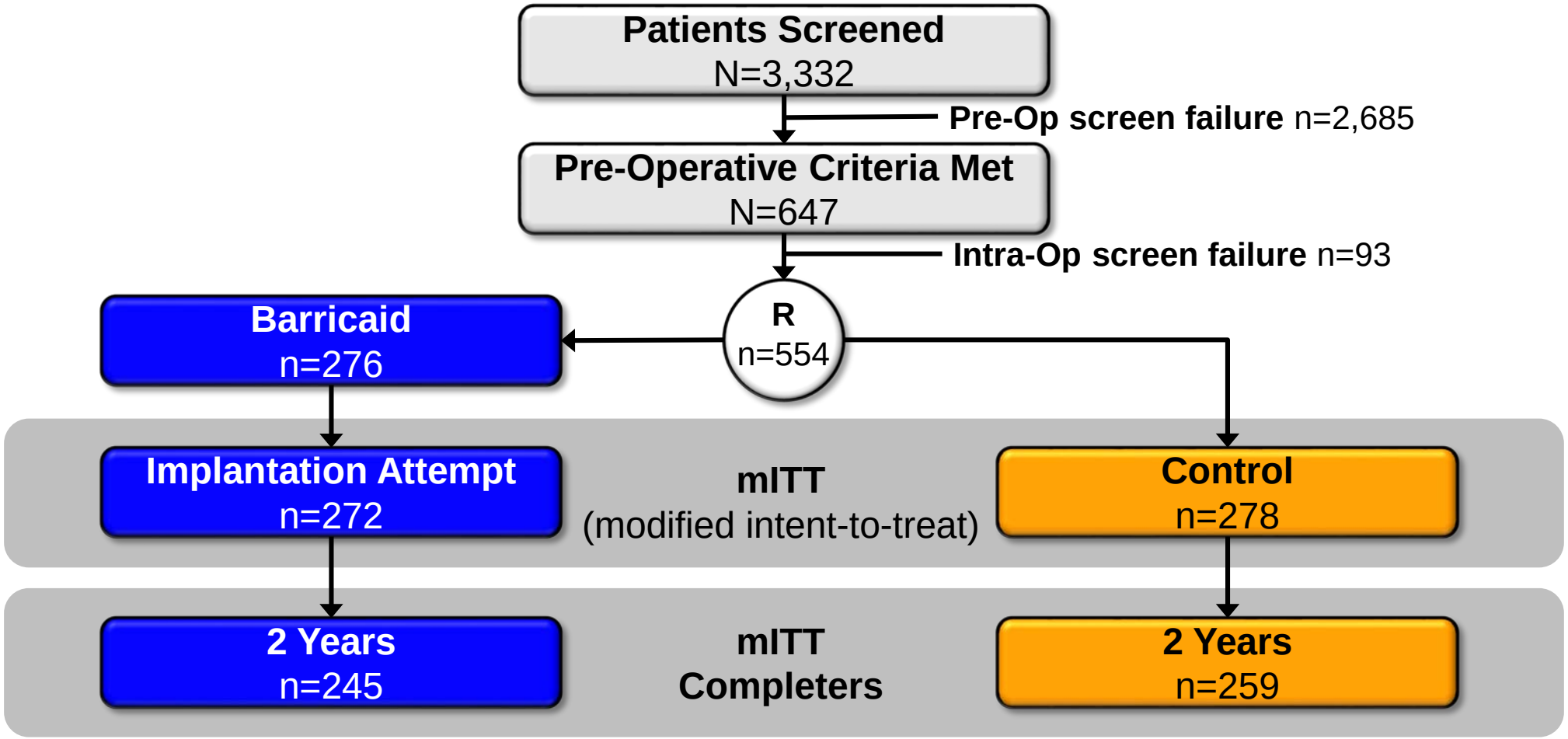
OLVG Hospital

Amsterdam, The Netherlands

Sites and Subjects

- 21 sites
  - Tier 1 countries: Austria, Belgium, France, Germany, The Netherlands, Switzerland
- 46 operating investigators
  - Orthopedic and neurosurgeons
- 3,332 patients screened
  - 554 patients enrolled (17%) over 46-month period
- ISO 14155, GCP, CFR Part 51 Compliant

Patient Accountability



>90% Accountability with Minimal Missing Data

Analysis Populations

Population	Analysis	Number of Patients	
		Barricaid	Control
mITT	Effectiveness	272	278
As-treated	Safety	267	283

- **mITT:** intended procedure was attempted
- **As-treated:** treatment actually received
  - 1 defect too medial
  - 1 nerve root injury
  - 3 mesh would not fully enter disc space

Comparison of Baseline Characteristics

Baseline Characteristic		Barricaid N=272	Control N=278
Age	Mean	43 years	44 years
Sex	Male	57%	62%
BMI	Mean	26.3 kg/m^2	26.3 kg/m^2
PROs, mean	VAS Leg	80.8	80.8
	VAS Back	56.6	55.7
	ODI	59.0	58.2
Index Level	L2/3	< 1%	< 1%
	L3/4	3%	2%
	L4/5	46%	36%
	L5/S1	51%	62%
Spondy Grade I		2.2%	2.9%

Balanced Between Groups,
Population Comparable to US Population

Intra-Operative Characteristics

Baseline Characteristic		Barricaid N=272	Control N=278
Defect size	Width, mean	7.8 mm	8.0 mm
	Height, mean	4.9 mm	4.9 mm
Nucleus removed	Volume, mean	1.26 cc	1.29 cc
Operative time	Median	67.0 min	47.0 min
Blood loss	Median	50.0 cc	50.0 cc

Intra-Operative Characteristics Had No Impact on Clinical Outcomes

Intra-Operative Characteristics

Intra-Operative Characteristic		Barricaid N=272	Control N=278
Surgical approach	**Created new defect**	**35%**	**39%**
	Through existing defect	**65%**	**61%**
Defect geometry (assessed after discectomy)	**Box**	**67%**	**57%**
	Other	**33%**	**43%**

Intra-Operative Characteristics Had No Impact on Clinical Outcomes

Superior Safety and Effectiveness: Co-Primary Endpoint Results

Endpoint (mITT)	Success Rate		Δ	Chi-squared p-value	Posterior probability of superiority
	Barricaid	Control			
No reherniation*	50.8%	30.1%	20.8%	< 0.001	> 99.99%
Composite	27.8%	18.1%	9.6%	0.010	99.48%

Barricaid is Superior for Both Co-Primary Endpoints

*Assessed by core lab and includes asymptomatic reherniation

Comprehensive Exploratory Analyses

Baseline:

- Spondylolisthesis Grade
- Prior procedures
- Device generation
- Patient blinding

Intra-Operative:

- New or existing defect
- Defect width
- Defect geometry
- Carragee classification
- Blood loss
- OR time
- Disc volume removed

Baseline and Intra-Operative Characteristics Had No Impact on Clinical Outcomes

Cohort Comparison: Success in All Assessments

Grouping	Assessments	Success Criteria	p-value
Discectomy-specific Outcomes	VAS Leg	> 20 mm improvement	0.454
	ODI	> 15 point improvement	0.545
	Neuro	Maintenance or improvement	0.083
General Radiographic Outcomes	Spontaneous Fusion	None at index level	0.320
	Disc Height	Maintain > 75%	0.678
Barricaid-specific Outcomes	Reherniation	No reherniations	< 0.001
	SSI	No SSIs	0.007
	Device Integrity	No integrity observations	n/a

Cohort Comparison: Superiority in Device Specific Assessments

Grouping	Assessments	Success Criteria	p-value
Discectomy-specific Outcomes	VAS Leg	> 20 mm improvement	0.454
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Barricaid-specific Outcomes	**Reherniation**	**No reherniations**	**< 0.001**
	SSI	**No SSIs**	
	Device Integrity	**No integrity observations**	

Discectomy-Specific Outcomes: No Difference in Pain/Function/Neuro

Grouping	Assessments	Success Criteria	p-value
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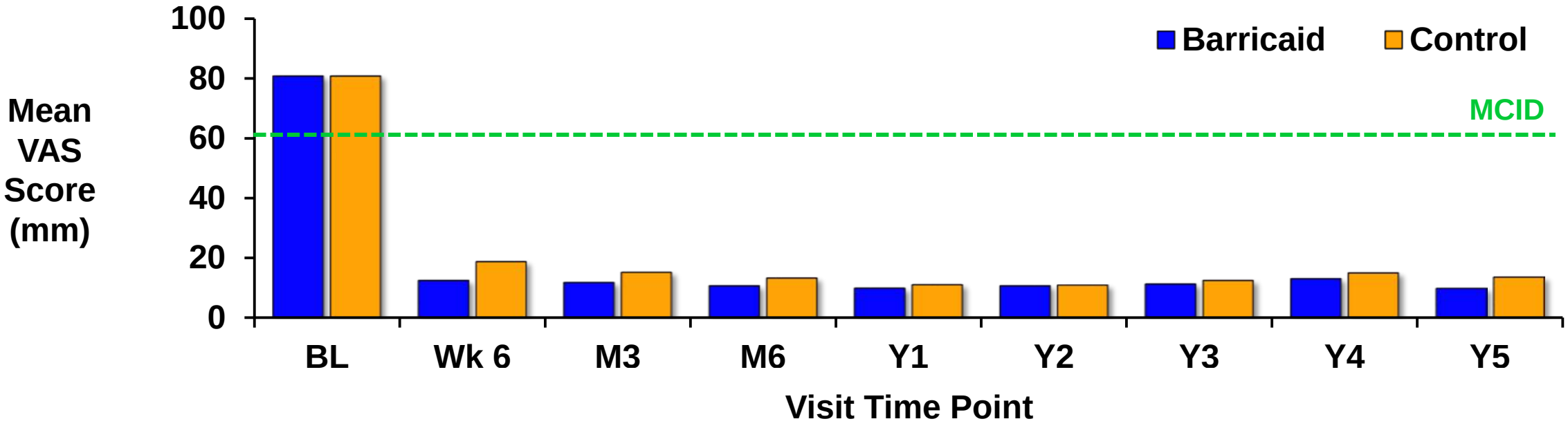
VAS Leg (Ipsilateral) Success

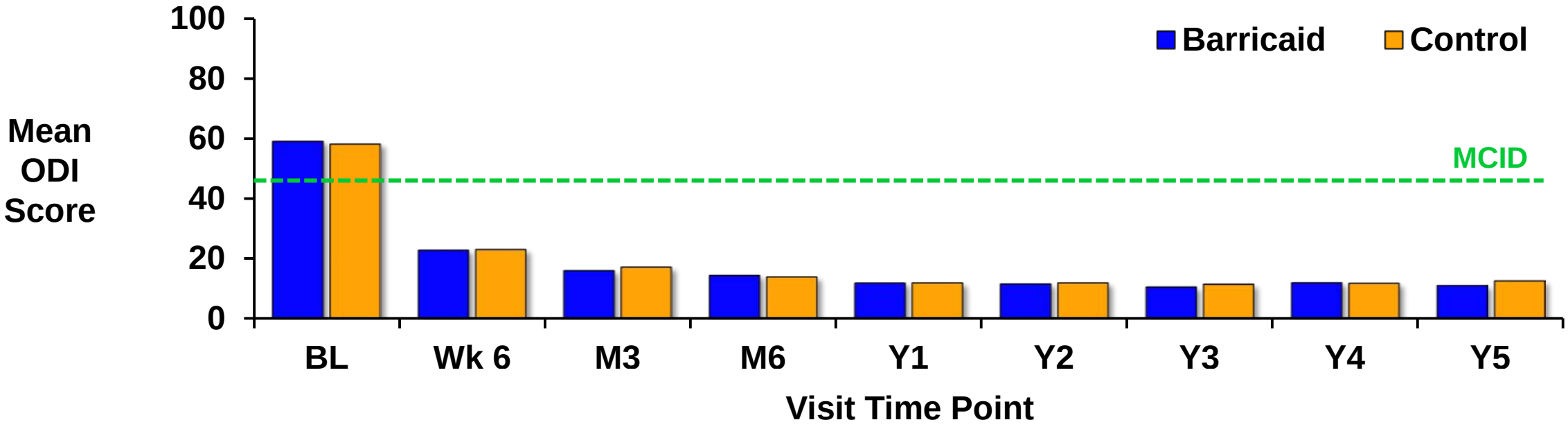
2-Year Results (mITT)	Barricaid	Control	Chi-squared p-value
% Success	94.7%	96.2%	0.454



Barricaid (n)	272	258	255	247	240	227	164	98	50
Control (n)	278	261	253	241	230	211	134	95	54

ODI Success

2-Year Results (mITT)	Barricaid	Control	Chi-squared p-value
% Success	93.4%	94.8%	0.545



Barricaid (n)	272	259	255	248	240	228	164	99	49
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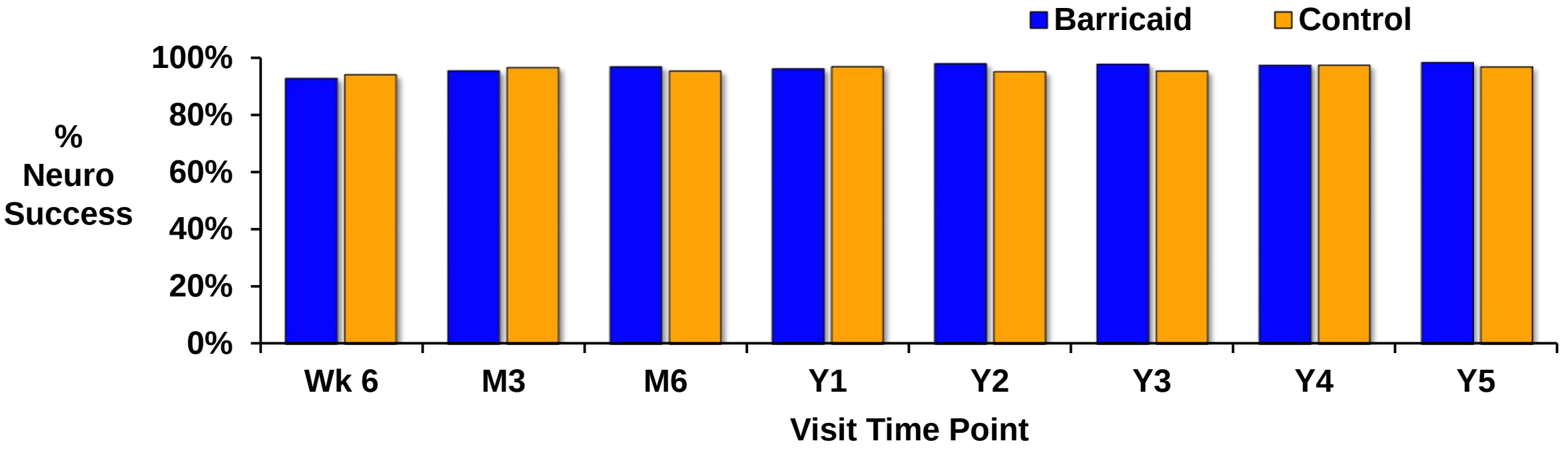
Neurological Success



Barricaid (n)	266	267	254	261	252	181	118	62
Control (n)	271	263	261	260	251	173	114	62

> 95% Free From Neurological Deterioration at 2 Years

General Radiographic Outcomes: No Differences

Grouping	Assessments	Success Criteria	p-value
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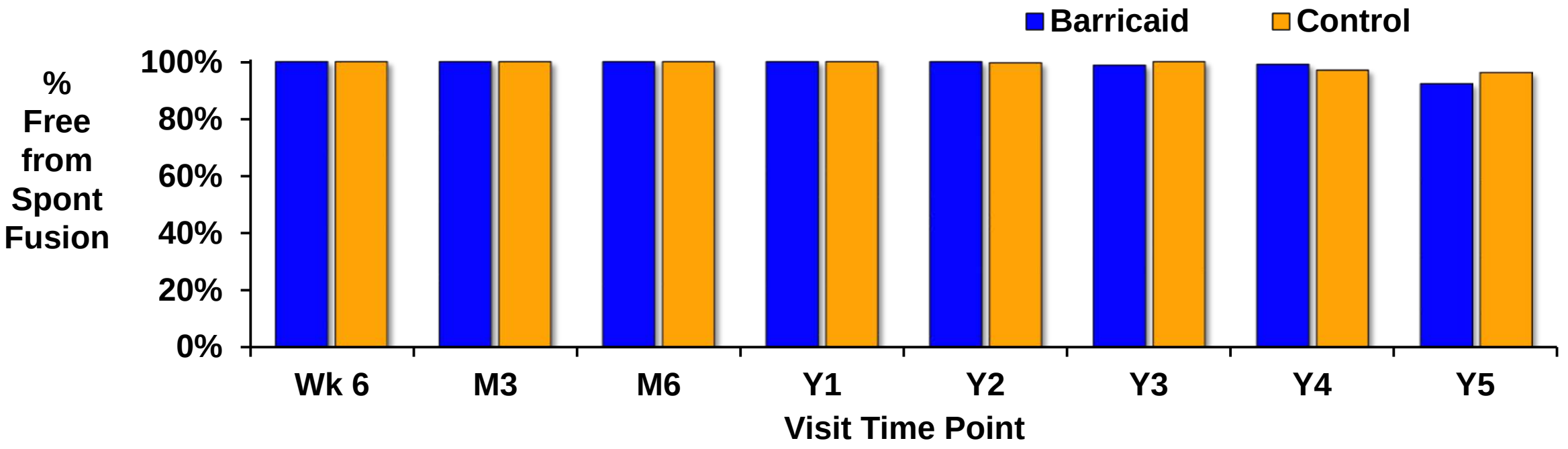
	Device Integrity	No integrity observations	n/a

Freedom from Spontaneous Fusion

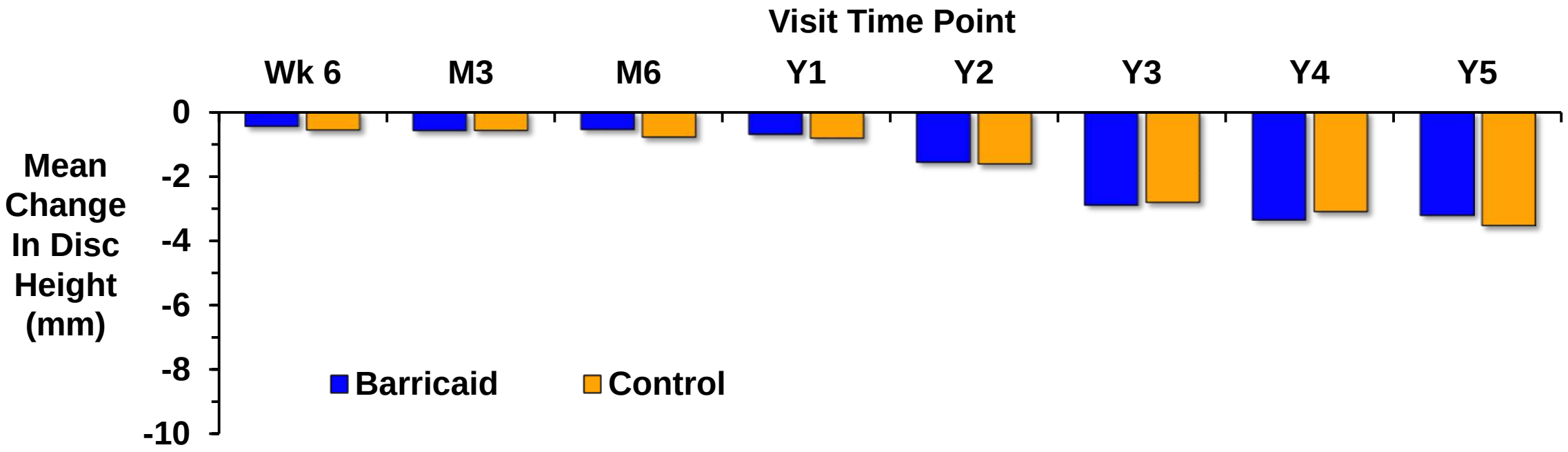


Barricaid (n)	263	262	256	260	249	169	109	53
Control (n)	266	259	257	260	252	166	105	53

No Difference From Control (p=0.320)

Disc Height Success

2-Year Results (mITT)	Barricaid	Control	Chi-squared p-value
Maintenance of Disc Height	65.4%	67.3%	0.678

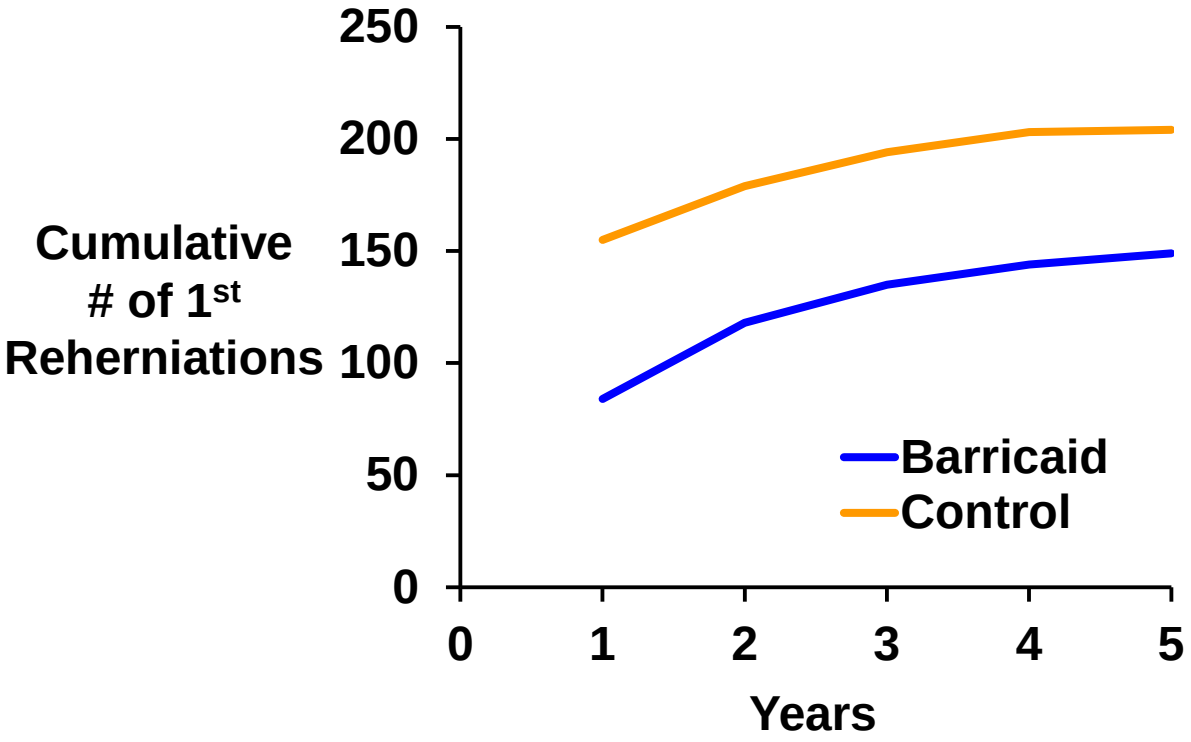


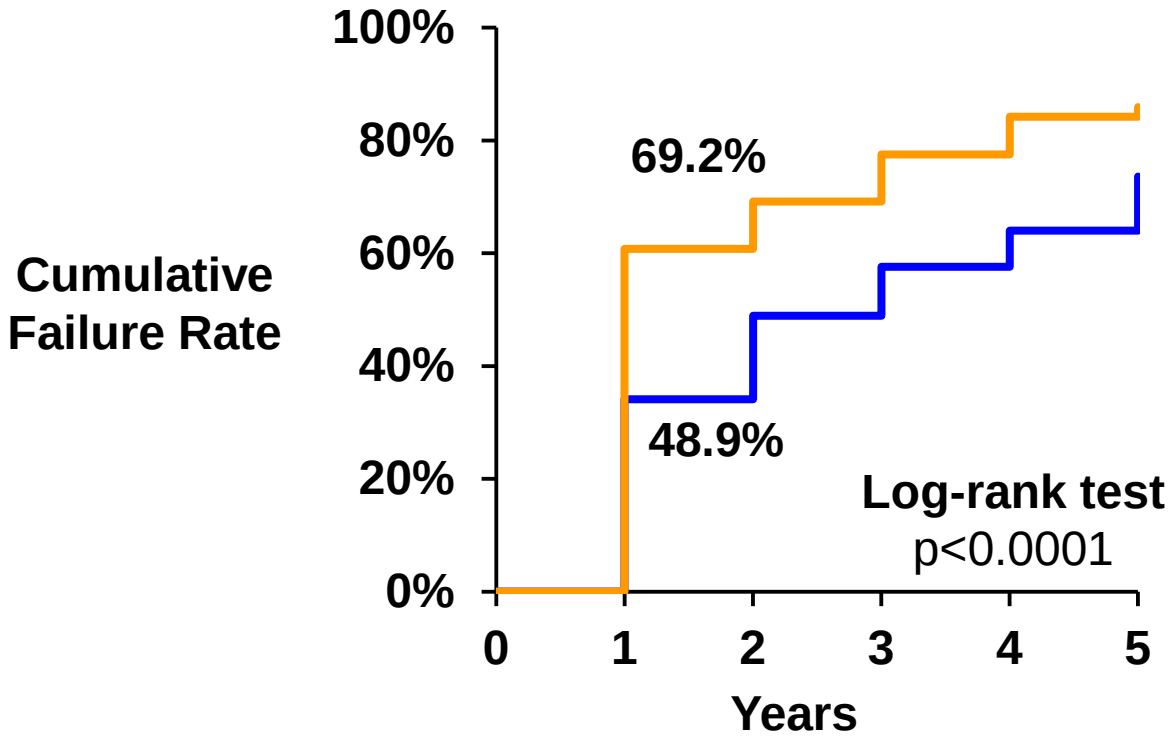
Barricaid (n)	246	240	233	229	211	141	85	40
Control (n)	242	236	228	216	196	119	80	41

Barricaid-Specific Outcomes: Superiority in Device Specific Assessments

Grouping	Assessments	Success Criteria	p-value
Discectomy-specific Outcomes	VAS Leg	> 20 mm improvement	0.454
	ODI	> 15 point improvement	0.545
	Neuro	Maintenance or improvement	0.083
General Radiographic Outcomes	Spontaneous Fusion	None at index level	0.320
	Disc Height	Maintain > 75%	0.678
Barricaid-specific Outcomes	**Reherniation**	**No reherniations**	**< 0.001**
	SSI	**No SSIs**	
	Device Integrity	**No integrity observations**	

All Reherniations



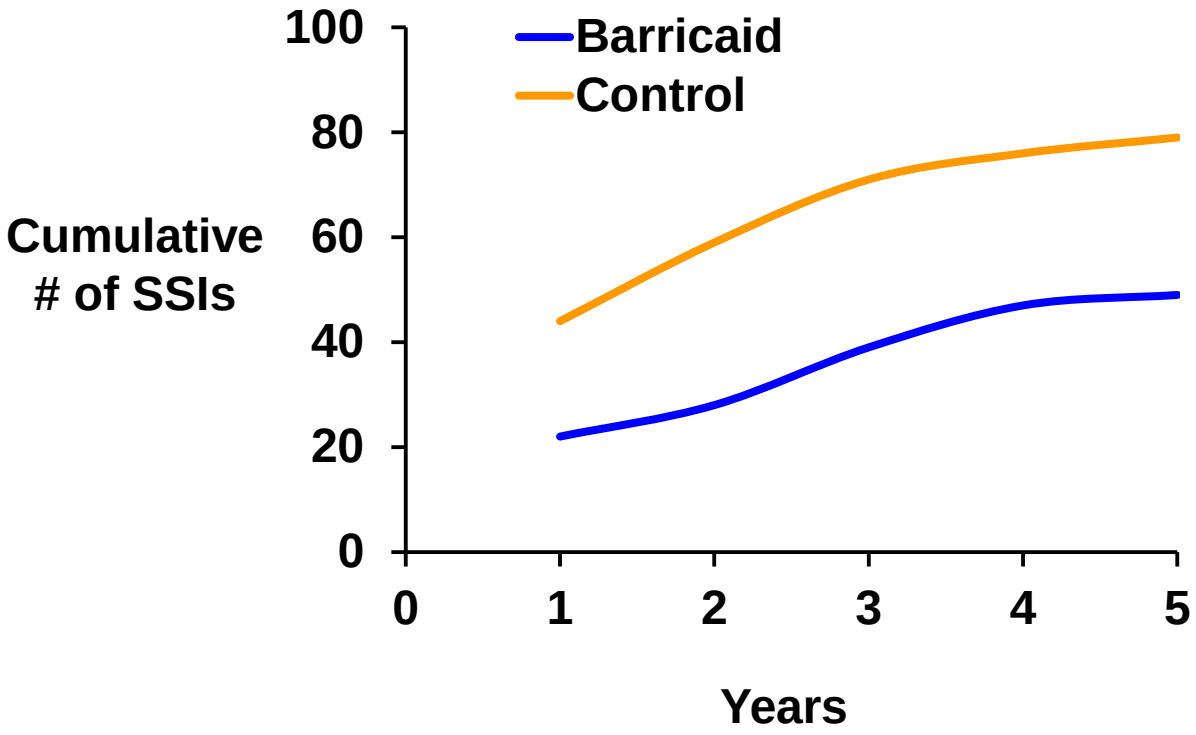


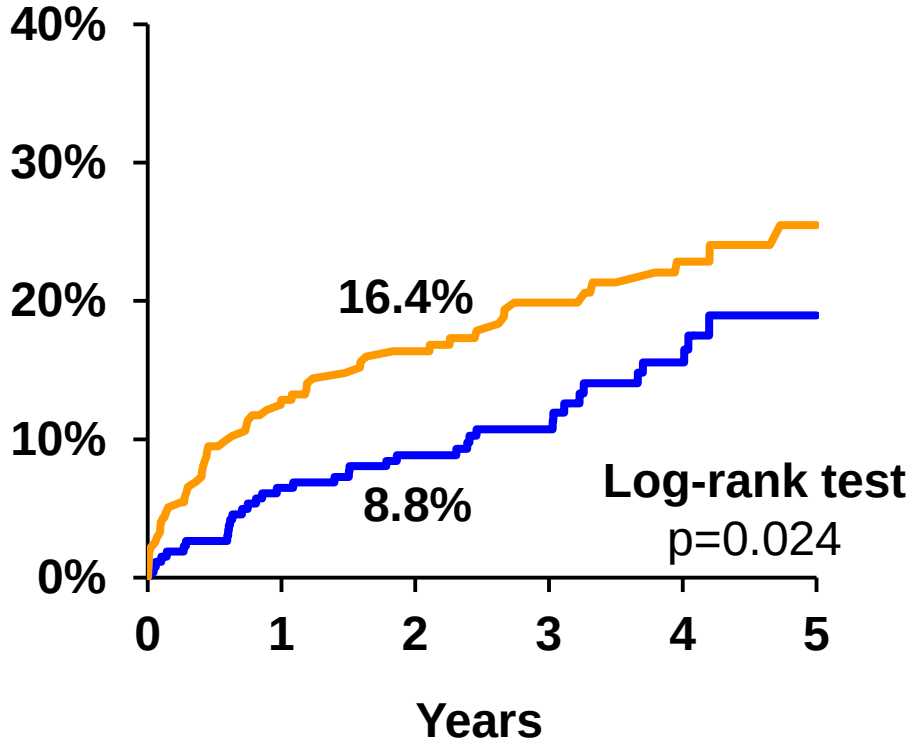
Number at risk

Barricaid	267	161	94	46	15
Control	278	98	59	27	9

Barricaid Superior in Preventing Reherniation through 5 Years (p < 0.0001)

Secondary Surgical Interventions (SSIs)



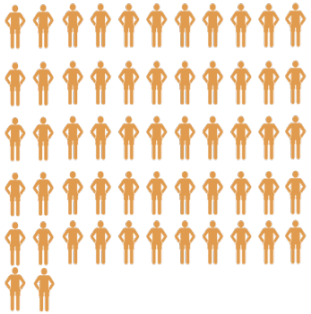


Number at risk

Barricaid	267	243	229	153	94
Control	278	232	202	143	91

Barricaid Superior in Preventing Reoperations through 5 Years (p=0.024)

Surgical Intervention Cascade

Reoperation	Barricaid n=49	Control n=79
First reoperation	38 	 57
Second reoperation	+9 	 +16
Third reoperation	+2 	 +4
Fourth reoperation	0	 +2

Patients with Initial Reoperation More Likely to Require Further Surgery

Survivorship Analysis Best for Presentation of Long-Term Data

- **Survival analyses**
  - Includes ALL known safety events through 5 years
  - Supported by FDA guidance*
- **Cross-sectional approach**
  - Limited to theoretically due population
  - Terminal failures carried forward but successes not counted until patient comes in
  - Ignores ~60% of known safety events

*** FDA's "Guidance Document for the Preparation of IDEs for Spinal Systems"**
ICH E9 Statistical Principles for Clinical Trials
The Prevention and Treatment of Missing Data in Clinical Trials: Panel on Handling Missing Data in Clinical Trials, National Academies Press, 2010

Reoperation with Barricaid No More Risky than Control

- Similar prevelance of fusion reoperation
  - 6.7% Barricaid vs. 4.7% Control (p=0.356)
  - No difference in operative time (p=0.255)

- Similar rate of complications in Barricaid reoperations compared to Control
  - Complications per reoperation:
  - 0.15 Barricaid vs. 0.25 Control (p=0.234)

Retrieval Study Conclusions

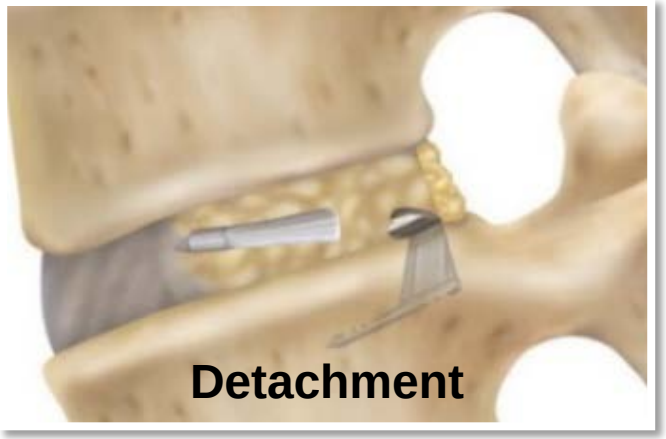
- 63 total commercial / clinical retrievals of implants and instruments
  - All study implant retrievals (n=21) evaluated per ASTM F561
- Occlusion component
  - Fraying difficult to differentiate in vivo from iatrogenic
  - FTIR demonstrates no material degradation
- 11 retrievals with tissue available for histology
  - 7 of 11 patients demonstrated presence of birefringent particles associated with device
- Expected host–implant responses with no evidence of infection and no association of inflammation with bone resorption

No Evidence of Active Osteolysis Associated with Particles or Infection

Radiographic Device Integrity Observations

Condition

- Fracture of anchor component
- Detachment of occlusion component



Migration

- Of anchor ≥ 2 mm
- Of occlusion component beyond posterior margin of disc space

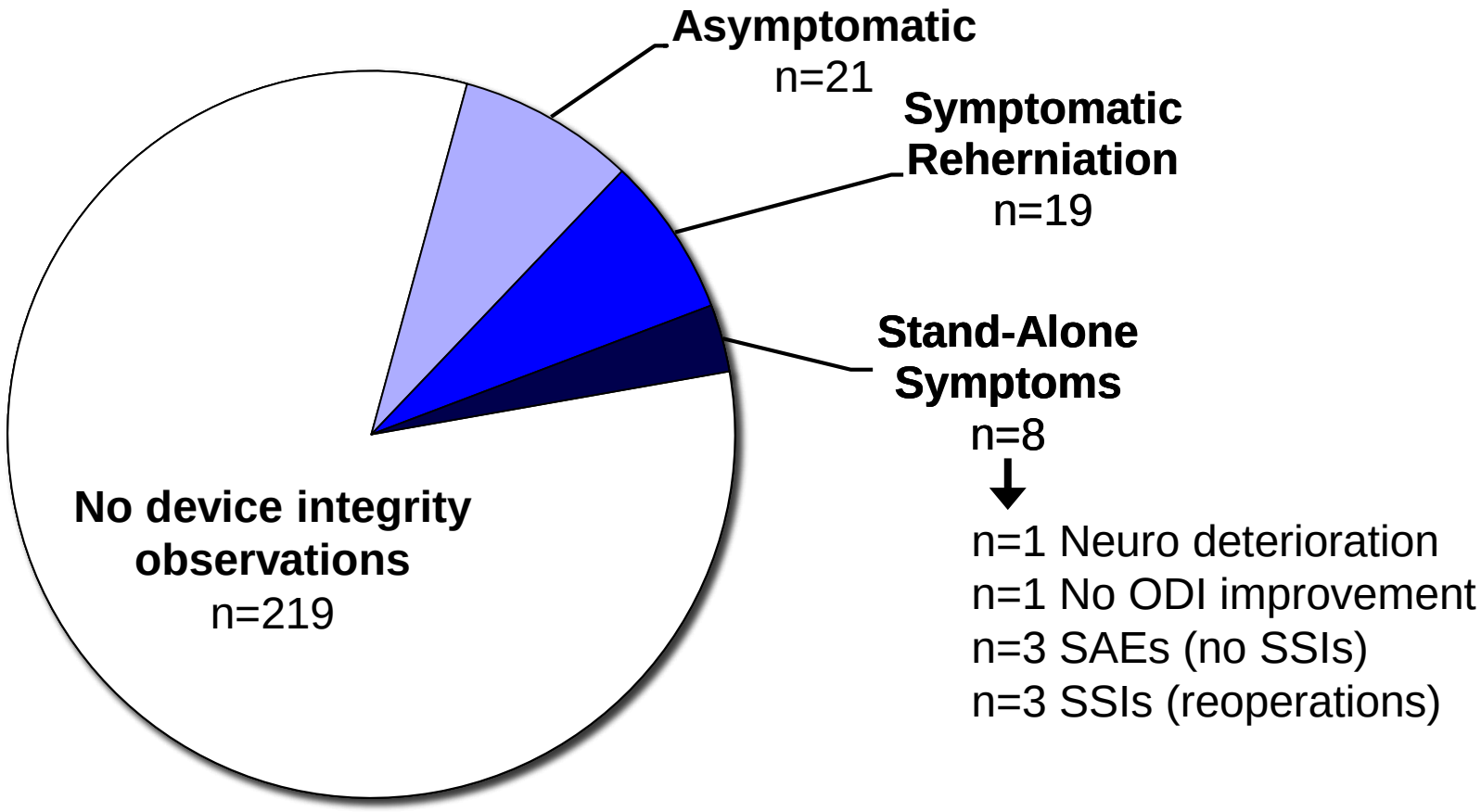
Device Integrity Observations

Device Integrity Observation	Through 2 Years		2–5 Years*	
	n	%	n	%
Total	**32**	**13.2%**	**16**	**9.8%**
Anchor Related				
Fracture and migration	2	0.8%	0	0.0%
Migration only	3	1.2%	1	0.6%
Occlusion Component				
Migration only	18	7.4%	12	7.3%
Detachment only	3	1.2%	2	1.2%
Detachment + migration	6	2.5%	1	0.6%

Mitigation Strategies Reduce Device Failure Rate

*** n=164 with at least one post-24 month visit in which integrity could be evaluated and integrity not observed in the first two years**

Clinical Impact of Device Integrity Observations



Many Device Integrity Observations are Asymptomatic

Patient-Focused Composite

Endpoint Appropriateness

- Endpoints were appropriate in clinical trial setting
  - Strict and detailed
  - Included asymptomatic radiographic observations
- Patient-focused endpoint
  - Captures surgeons' and patients' expectations
  - Aligns with other spine PMA composite endpoints

Post-Hoc Patient-Focused Composite

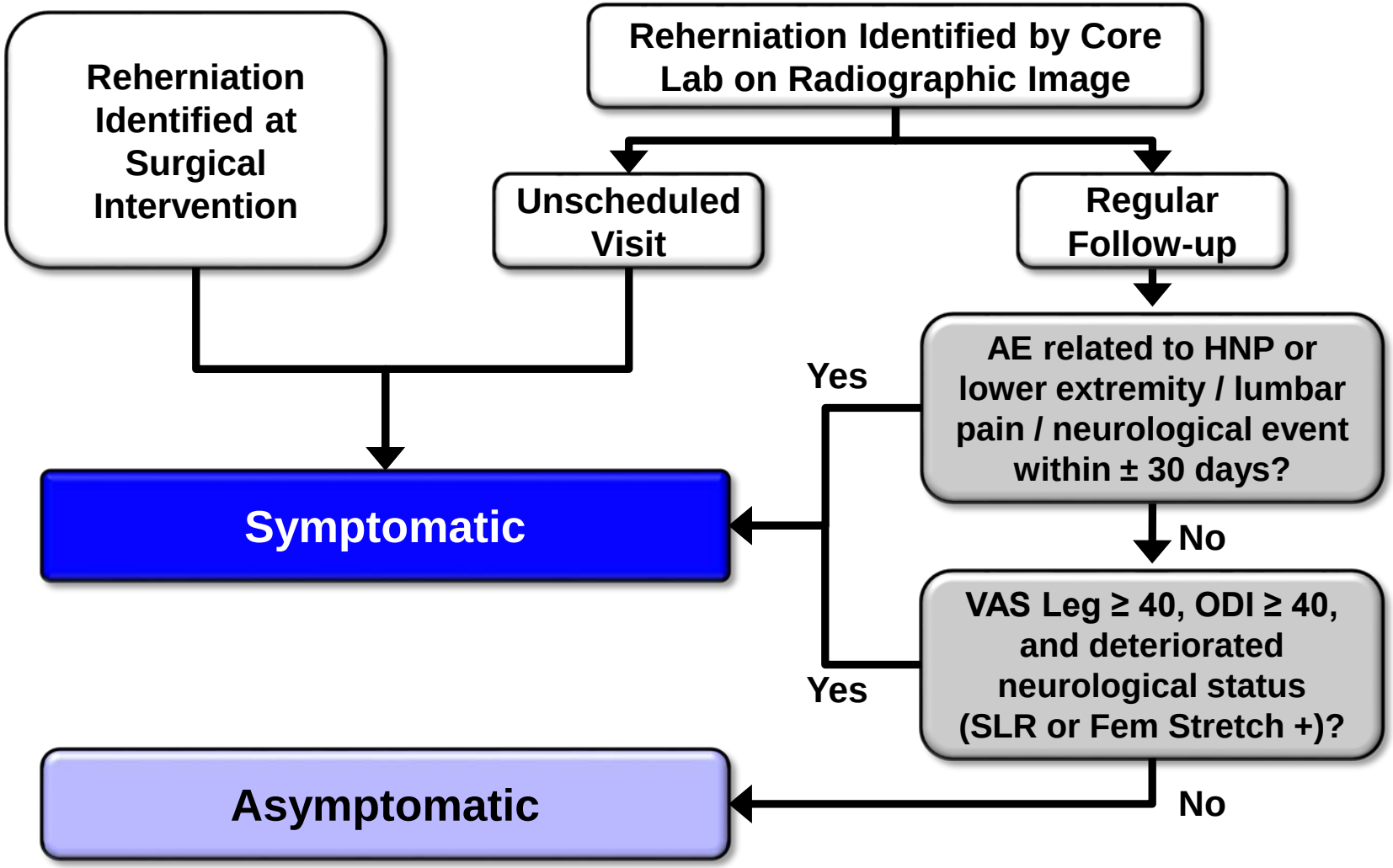
Grouping	Composite Endpoint (Per Protocol)	Patient-Focused Alternate Composite Endpoint
Discectomy-specific Safety and Effectiveness	VAS Leg	--
	ODI	ODI
	Neuro	Neuro
General Radiographic Outcomes	Spontaneous Fusion	--
	Disc Height	--
Barricaid-specific Safety and Effectiveness	Reherniation	Symptomatic Reherniation
	SSI	SSI
	Device Condition	SAEs Related to Device or Procedure

Endpoint Superiority

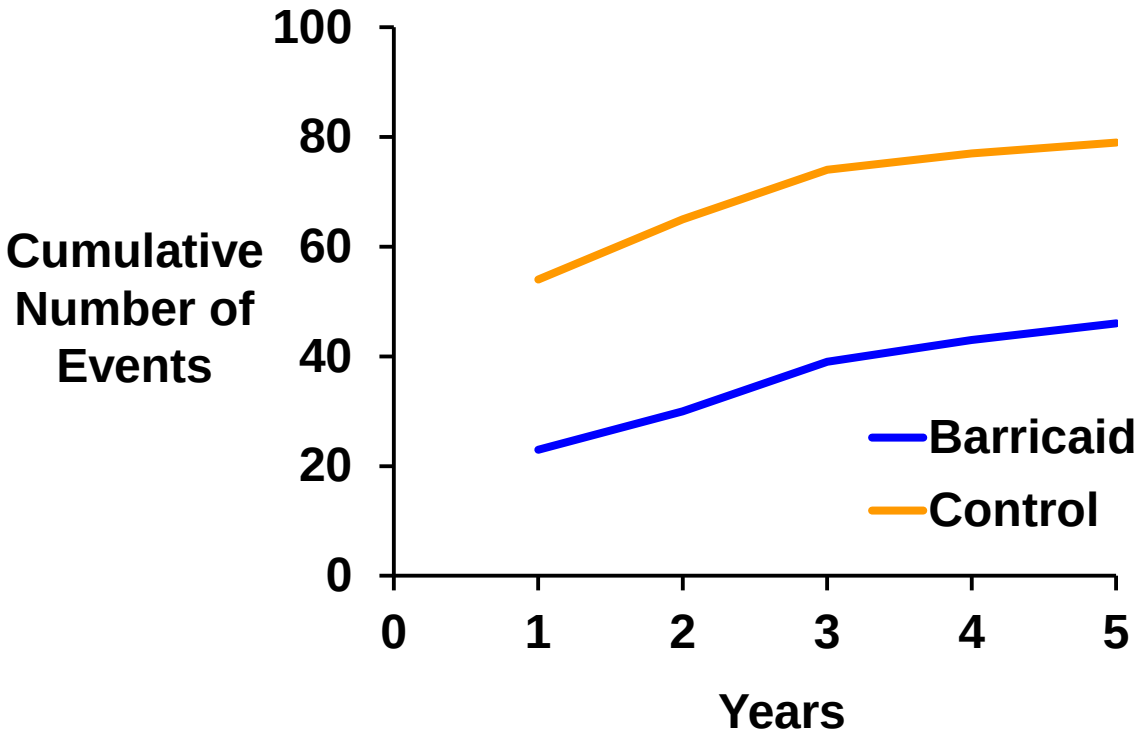
Endpoint (mITT)	Success Rate		Δ	Chi-squared p-value	Posterior probability of superiority
	Barricaid	Control			
No reherniation	50.8%	30.1%	20.8%	< 0.001	> 99.99%
Composite (Per Protocol)	27.8%	18.1%	9.6%	0.010	99.48%
Post-Hoc Patient-Focused Composite	75.9%	63.9%	12.0%	0.004	99.84%

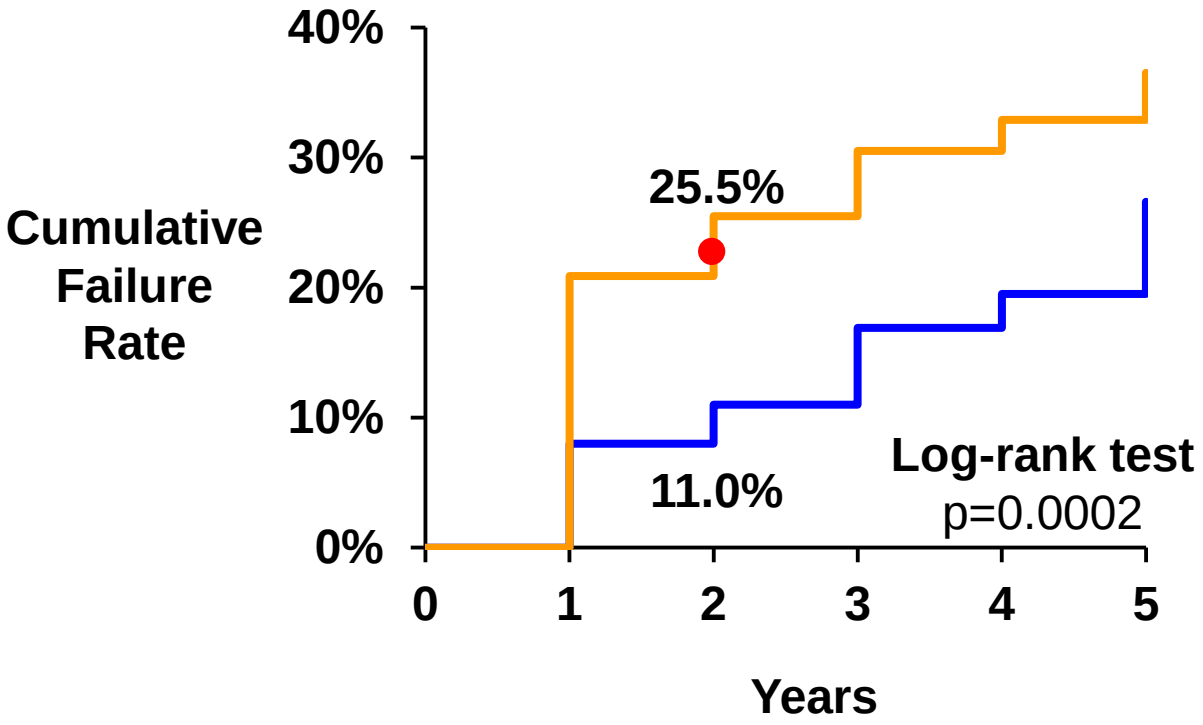
Superiority Demonstrated in Both a priori and Patient-Focused Composite

Classification of Symptomatic Reherniation



Symptomatic Reherniation





Number at risk					
Barricaid	240	206	138	83	26
Control	229	179	121	75	30

Barricaid Superior in Preventing Symptomatic Reherniation through 5 Years (p=0.0002)

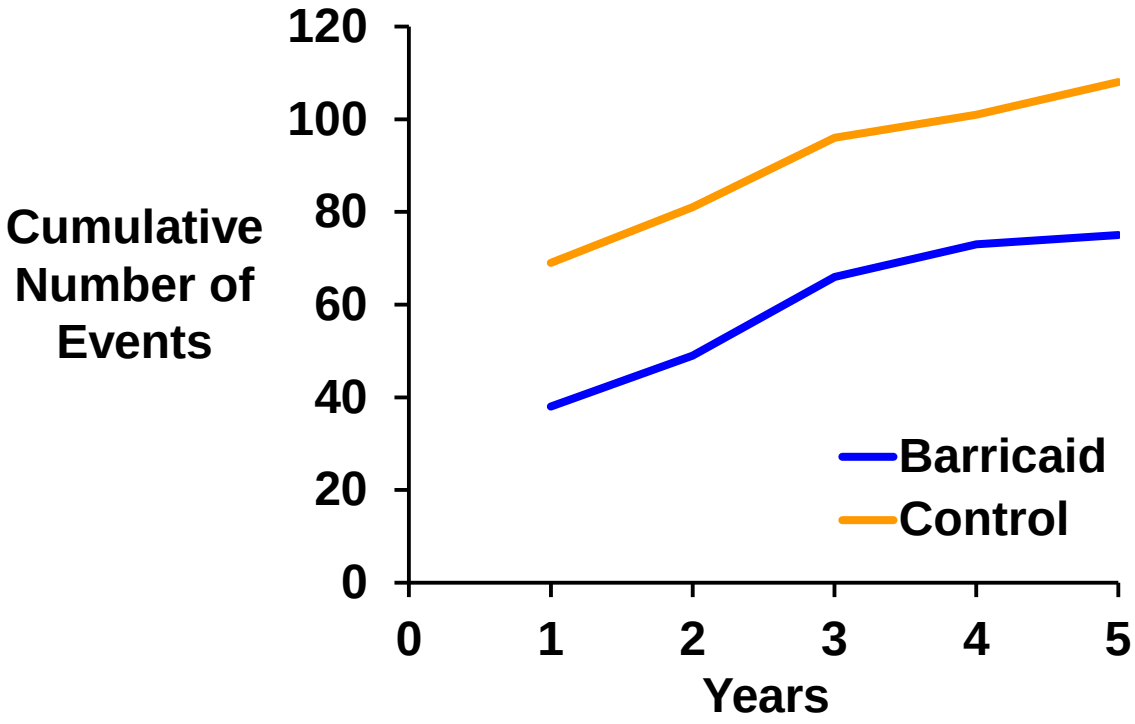
Summary of Adverse Events

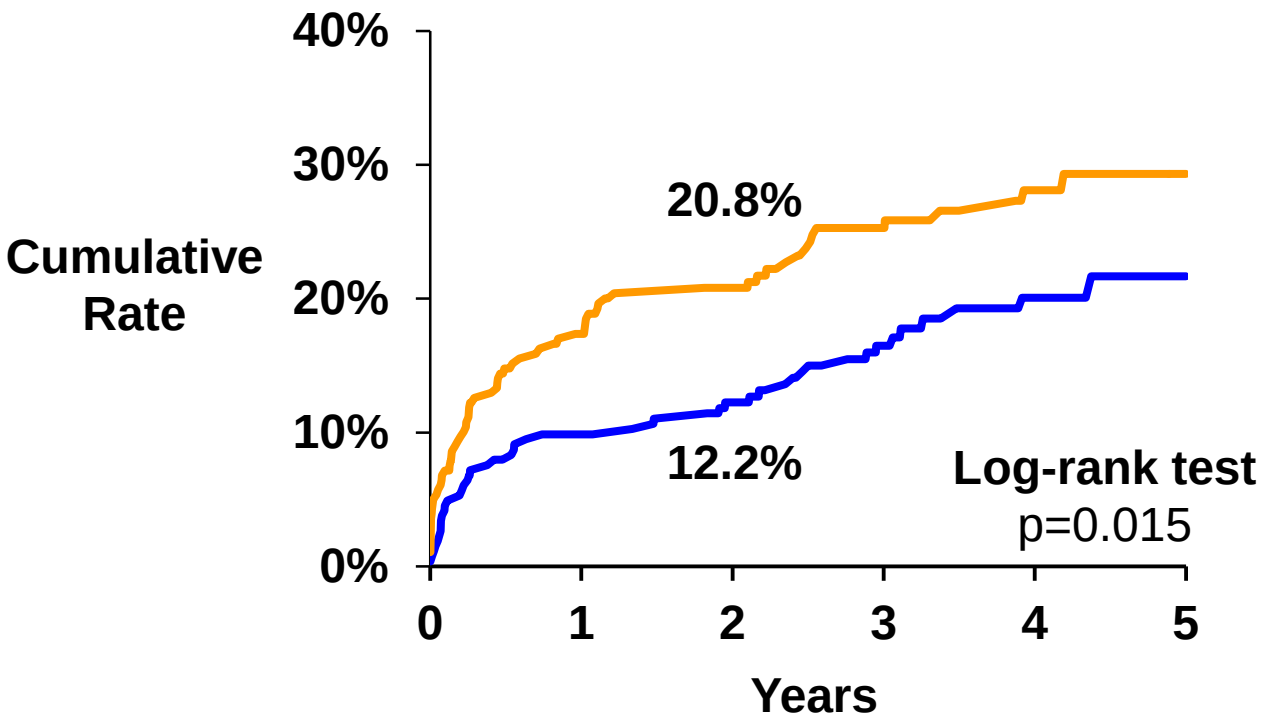
	Barricaid N=267			Control N=283			
	Events	Subjects	%	Events	Subjects	%	p-value
Any Adverse Event	626	222	83.1%	564	221	78.1%	0.161
Dev. or Proc. Related	378	185	69.3%	337	179	63.3%	0.149
Any Serious AE (SAE)	187	100	37.5%	190	116	41.0%	0.432
Dev. or Proc. Related	78	47	17.6%	108	71	25.1%	0.038
Death (Unrelated to Dev. or Proc.)	1	1	0.4%	0	0	0.0%	0.486

Significantly Greater Rate of Related SAEs in Control Group

All available data at Year 5

Related Serious Adverse Events



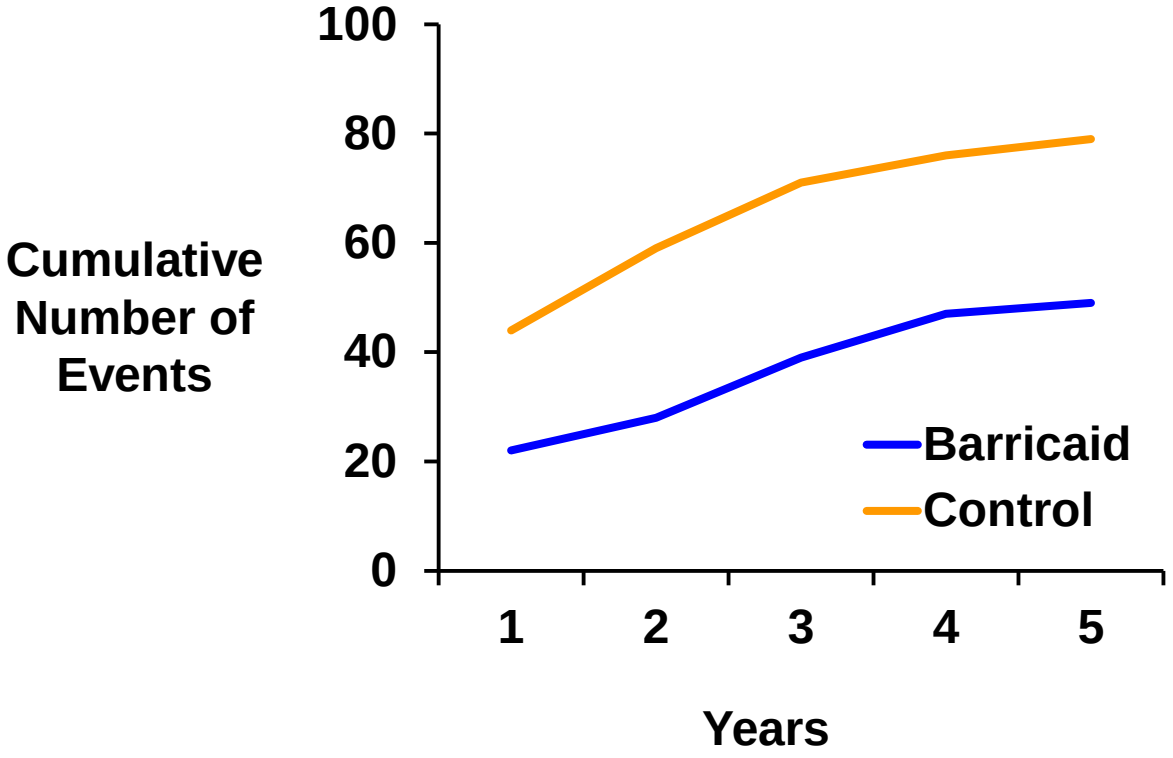


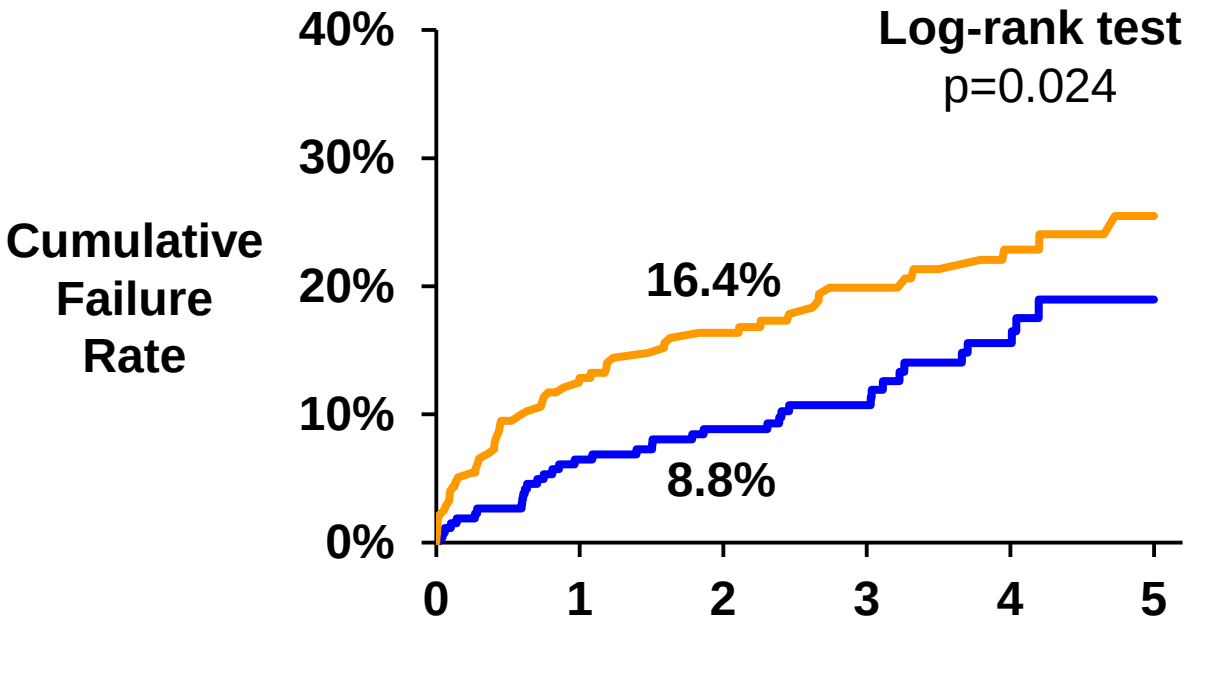
Number at risk

Barricaid	267	234	210	144	87
Control	283	222	193	135	84

Significantly Fewer Related SAEs with Barricaid through 5 Years (p=0.015)

Secondary Surgical Interventions (SSIs)



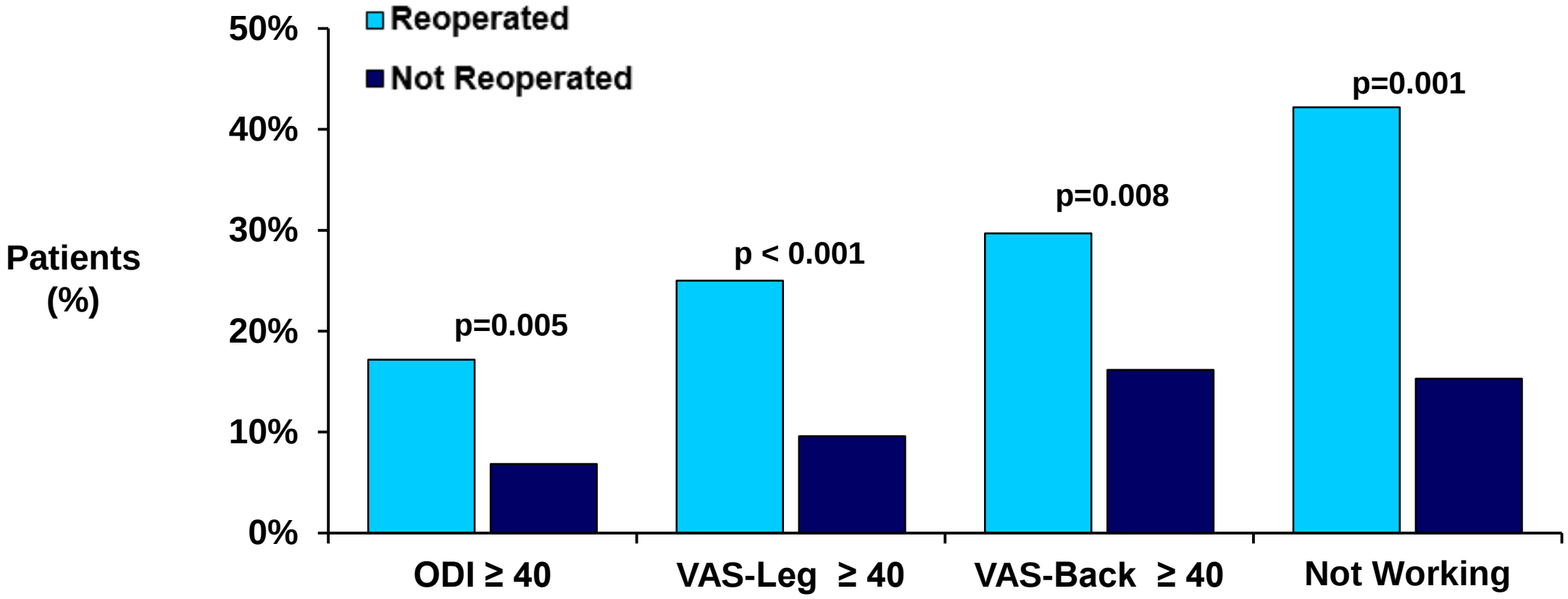


Number at risk

Barricaid	267	243	229	153	94
Control	278	232	202	143	91

Barricaid Superior in Preventing SSI through 5 Years (p=0.0243)

Significant Disability After Reoperation at 2 Years



Reoperated Patients Report More Chronic Pain, and Disability than Non-Reoperated Patients

Barricaid Demonstrated Superiority to Control

	Barricaid	Control	Chi-squared p-value
Symptomatic reherniations	11.2%	25.4%	< 0.001
SSIs (reoperations)	8.6%	16.2%	0.007
Related SAEs	12.9%	20.5%	0.016

Patient Success Driven by Barricaid Intended Use

Data at Year 2

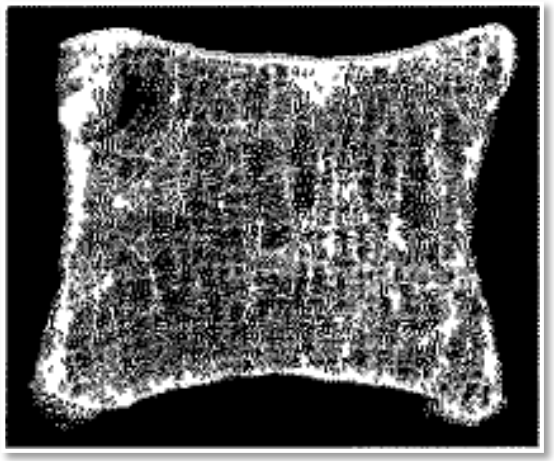
Endplate Change (EPC) Observations & Evaluation

Adisa Kuršumović, MD

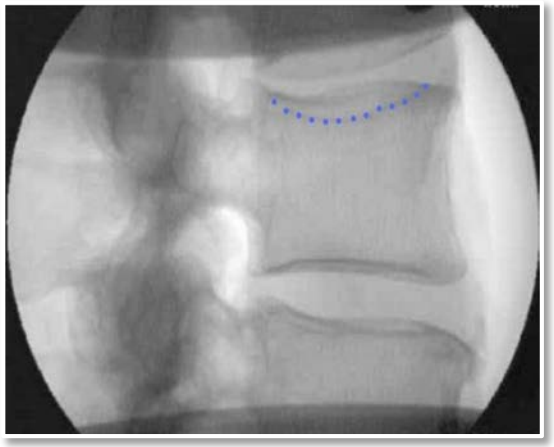
Donauisar Klinikum Deggendorf

Deggendorf, Germany

Lumbar Vertebral Endplate: Composition



- Layer of bone covered by cartilage on top and bottom of each vertebra
- Cortex measures 0.06 mm–1.08 mm[1]
- Perforated to support nutrient transport



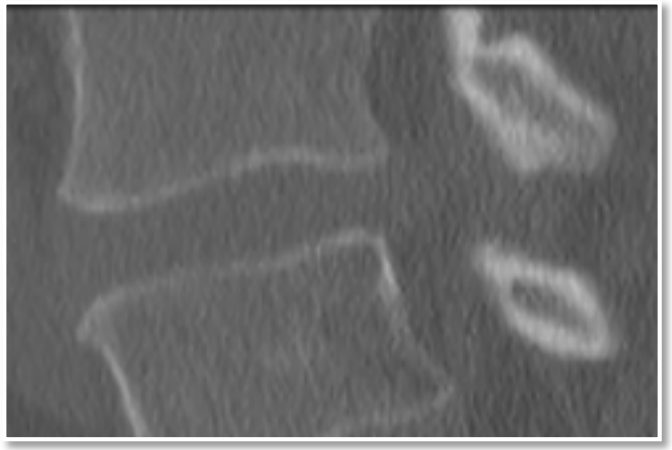
- Deflects under load
  - 2.15 mm (range: 0.66–3.85 mm)

1. Jackman (2014)

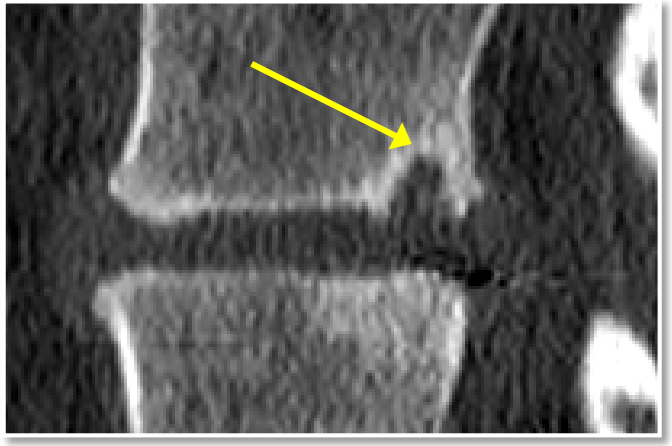
What Are Endplate Changes?

- Endplates degenerate naturally over time[1]
- Discectomies can cause or increase EPCs, regardless of anular closure device use[2]
- Visible defects in endplates have no clinical consequence for most people

No Endplate Change



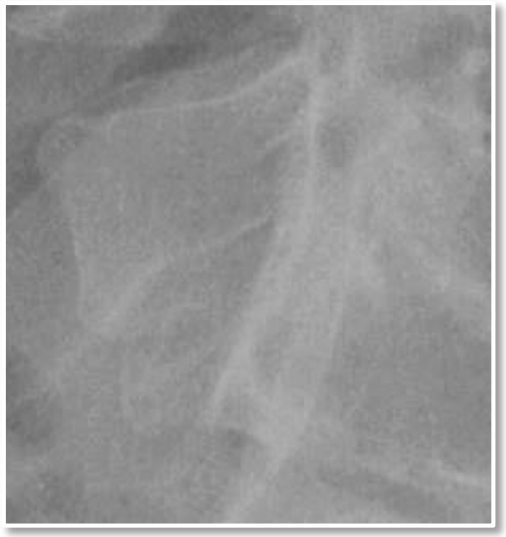
Endplate Change



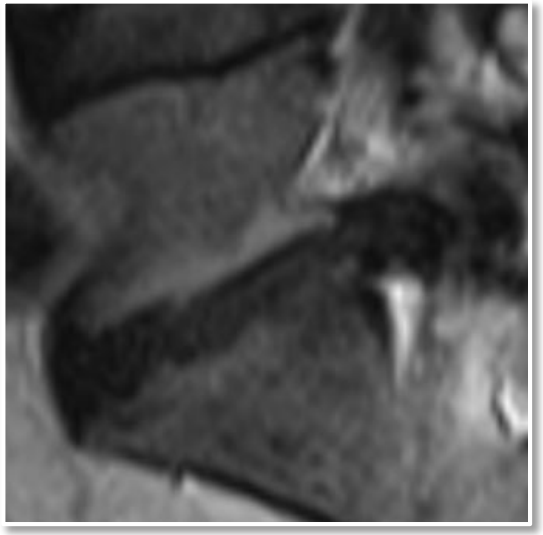
1. Wang (2012); 2. Weiner (2015)

Endplate Changes in Various Modalities

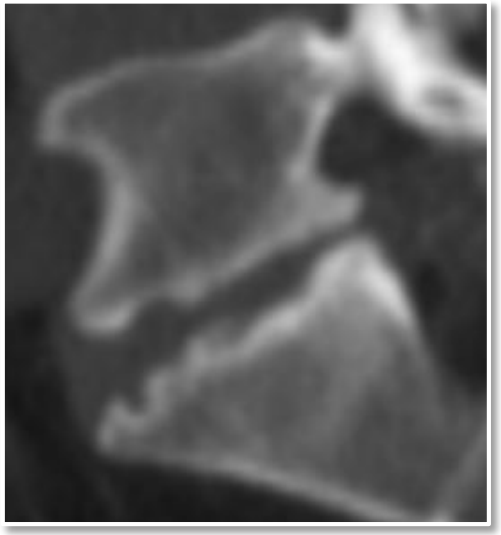
X-Ray



MRI



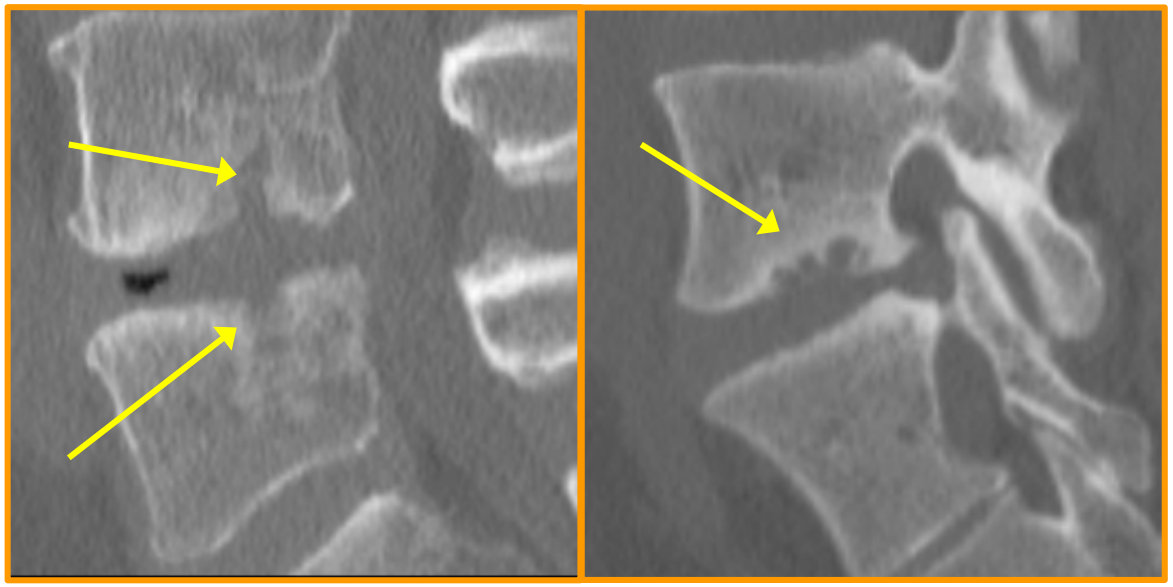
CT



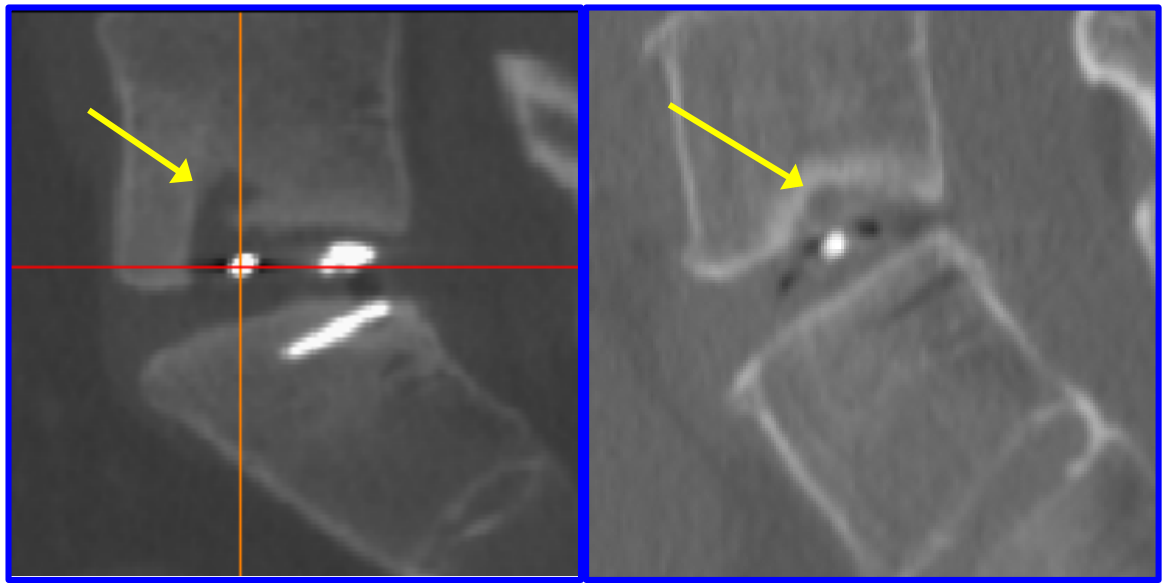
Endplate Changes More Easily Visualized Using Longitudinal CT Imaging

Endplate Changes Observed in Both Study Groups

Control (1 Year)



Barricaid (1 Year)



Conclusions From Endplate Change Analyses

- EPCs observed in both groups
  - Higher frequency and larger average size in Barricaid
  - Range of sizes similar between groups
- Larger EPCs grow more slowly
  - Plateau in size
  - No risk to vertebral integrity
- No negative clinical impact associated with Barricaid and EPC

Radiographic Assessments and Analyses: 50,000 Radiographic Images

Quantitative Assessments	Qualitative Assessments
■ Number ■ EPC and vertebral body dimensions ▪ Axial, coronal and sagittal planes ■ Volume estimation for EPC and vertebral bodies	■ Sclerotic margin characterization ■ Perilesional reactivity ■ Septation assessment ■ Posterior cortex involvement ■ Mineralization/high attenuation within EPC ■ EPC location in sagittal and axial planes (5x5 grid)

Analyses Included Absolute Size, Growth Rate, Change in Growth Rate, Stability (Qualitative and Quantitative Features), and Clinical Correlation

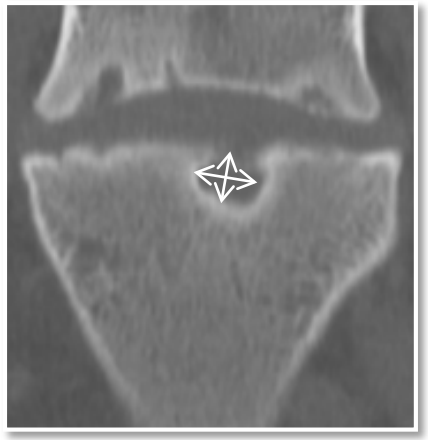
Analysis of Sub-Groups of Interest

- EPCs with mesh subsidence
  - FDA describes these as “lytic”

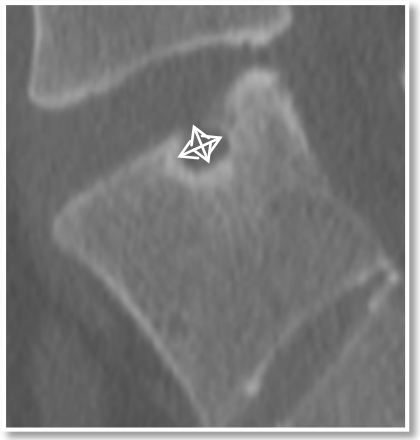
- Large EPCs
  - Area > 100 mm^2
    (upper ~20% of EPC sizes)

Validated Size Measurements

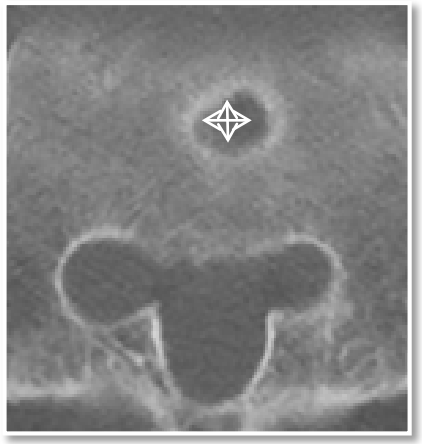
- Size measured in each plane where EPC appears largest[1]



Coronal



Sagittal



Axial

- Independent pilot study validated area to volume linear relationship using direct measurement from 3D reconstructions (r=0.84)

1. Weiner (2015)

Results of Endplate Change Analyses

Quantitative & Qualitative Results

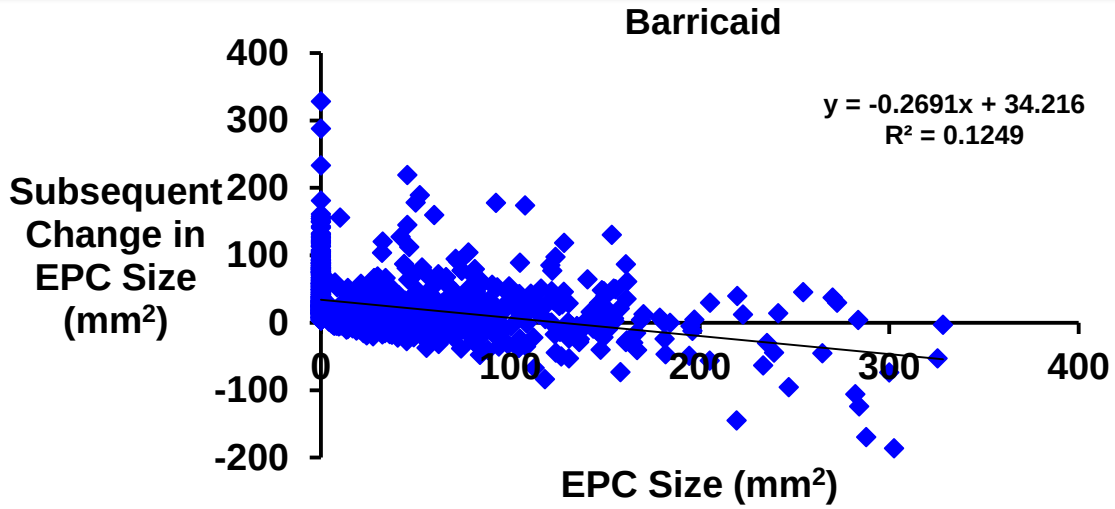
	Barricaid N=267	Control N=283
Total Patients	235	113
Total EPCs	483	190
Pre-op	63	55
Post-op	420	135
Patients with EPCs	88%	40%
Large EPCs (> 100 mm^2) (% of all EPCs)	22%	22%
EPCs with Mesh Subsidence (% of all EPCs)	18%	n/a
EPC Size at 2 years (mm^2)		
Mean	60.6	51.4
Range	3.1 – 325.4	3.1 – 398.4

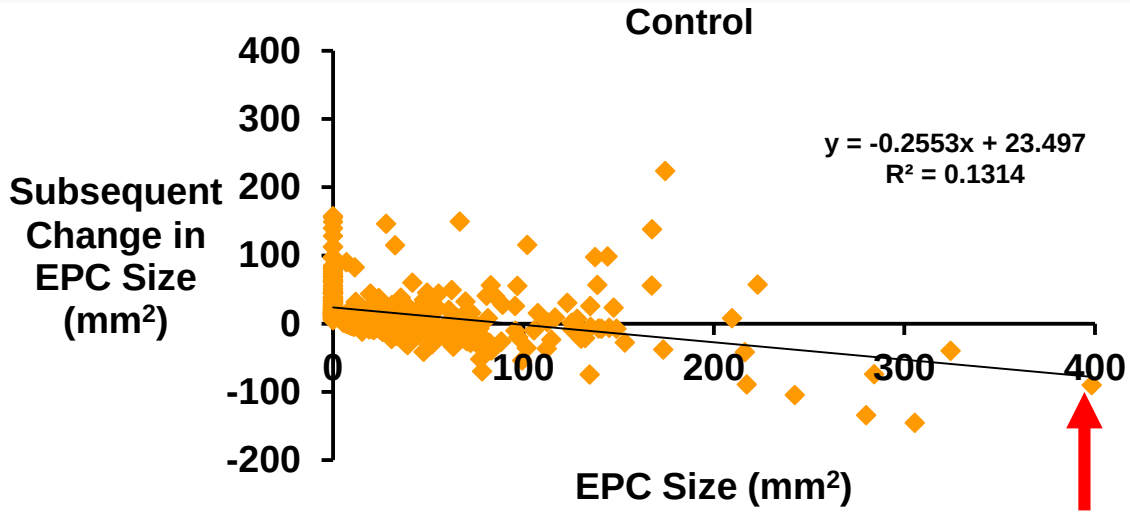
EPCs Observed in Both Arms, Pre- and Post-Op

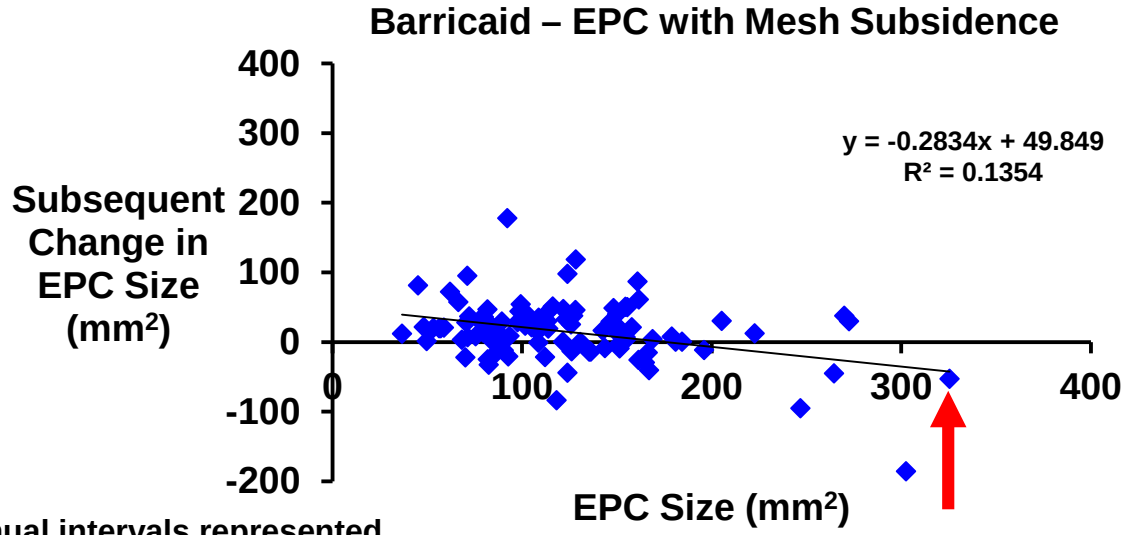
EPC Root Cause Summary

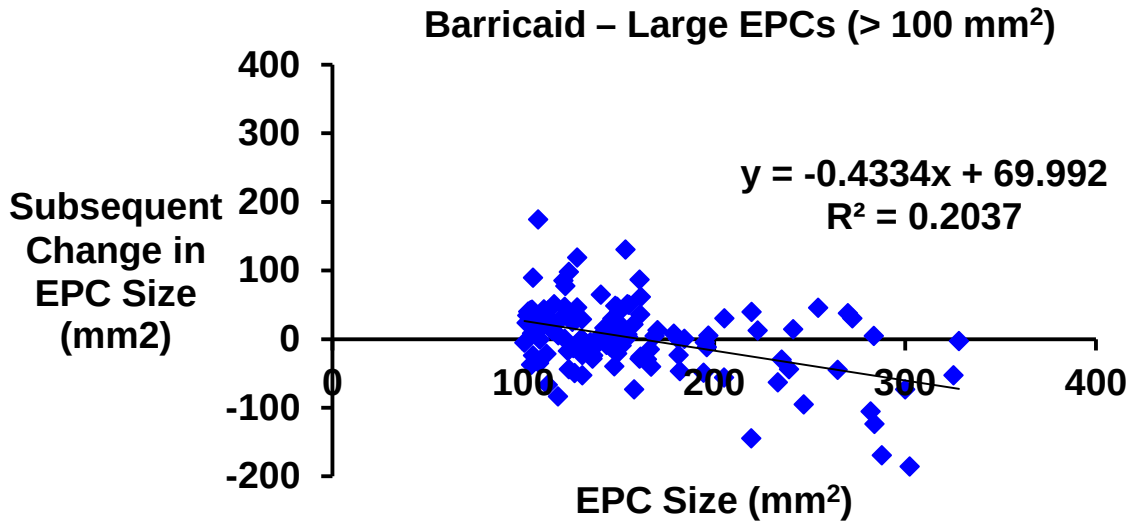
- Explant histology and study imaging:
  - No evidence of infection or particle-induced osteolysis
- Mechanical root cause:
  - Pre-operative: Herniation often includes endplate fragments
  - Post-discectomy: May be caused by discectomy or loss of disc material
  - Barricaid: Intradiscal mechanics
  - Baboon
    - Barricaid: Device too large for disc space
    - Control: EPCs observed (though more limited)

Large EPCs Grow More Slowly



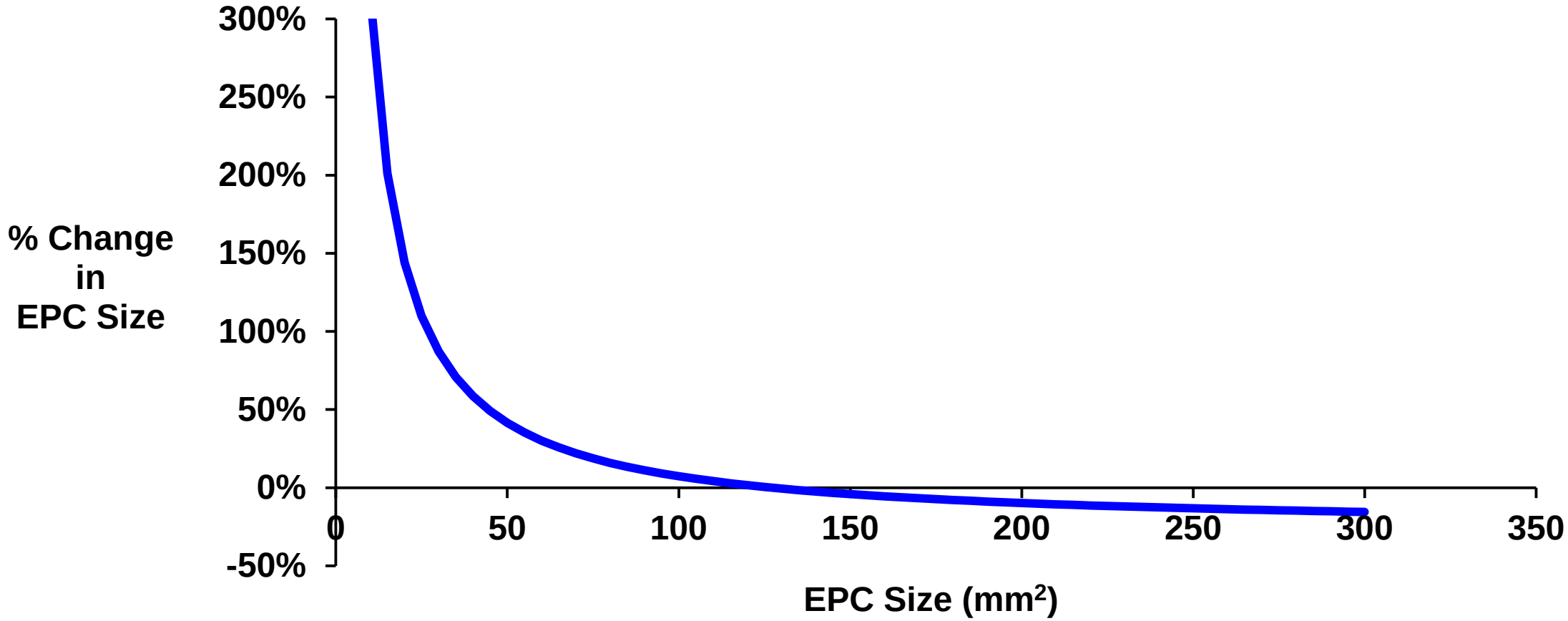






All annual intervals represented.

Change in EPC Size Decreases for Larger EPCs



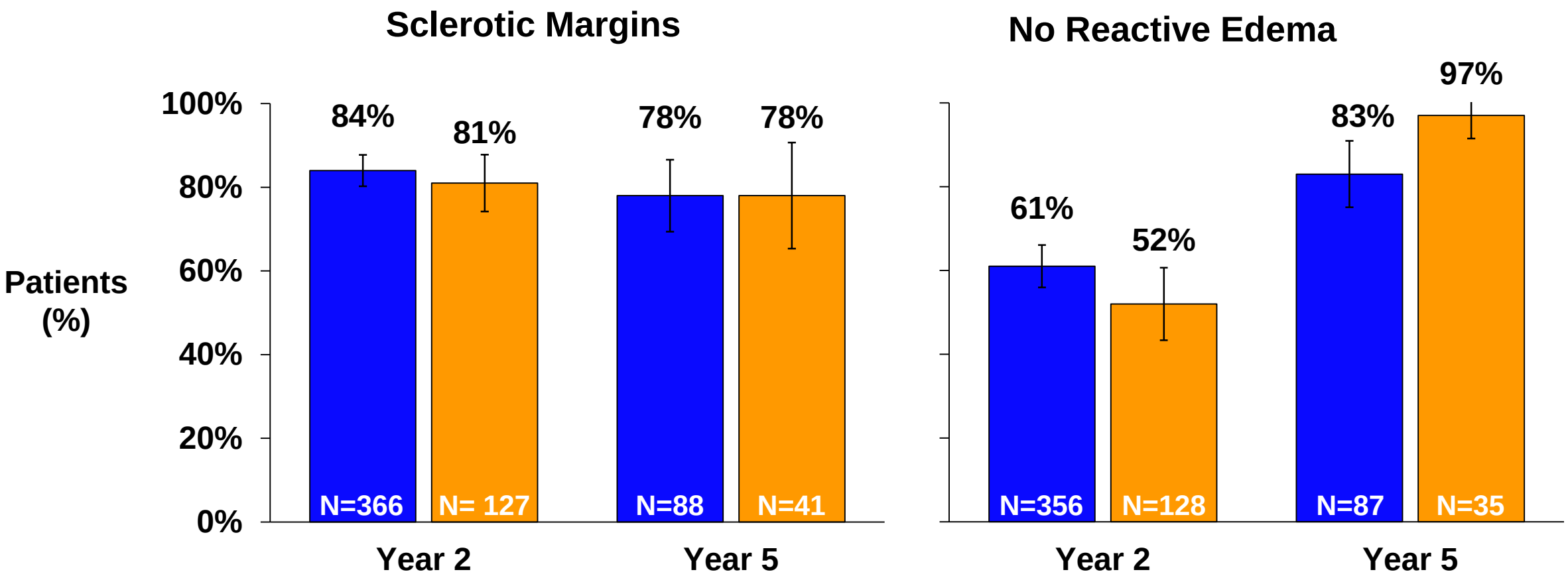
Larger EPCs Grow More Slowly, Plateau or Decrease in Size

EPC Size Below Risk Threshold for Loss of Vertebral Body Integrity

- Risk of vertebral collapse begins when ~50% of vertebral body is compromised[1]
- Largest EPCs occupy < 8% of vertebral body volume
  - No further growth at later follow-ups
  - Far below risk threshold for loss of vertebral body integrity
- No vertebral body fractures have been reported by sites nor observed by core lab

1. Taneichi (1997); Dimar (1998); Georgy (2008); Campos (2014)

Healing Qualitative Characteristics

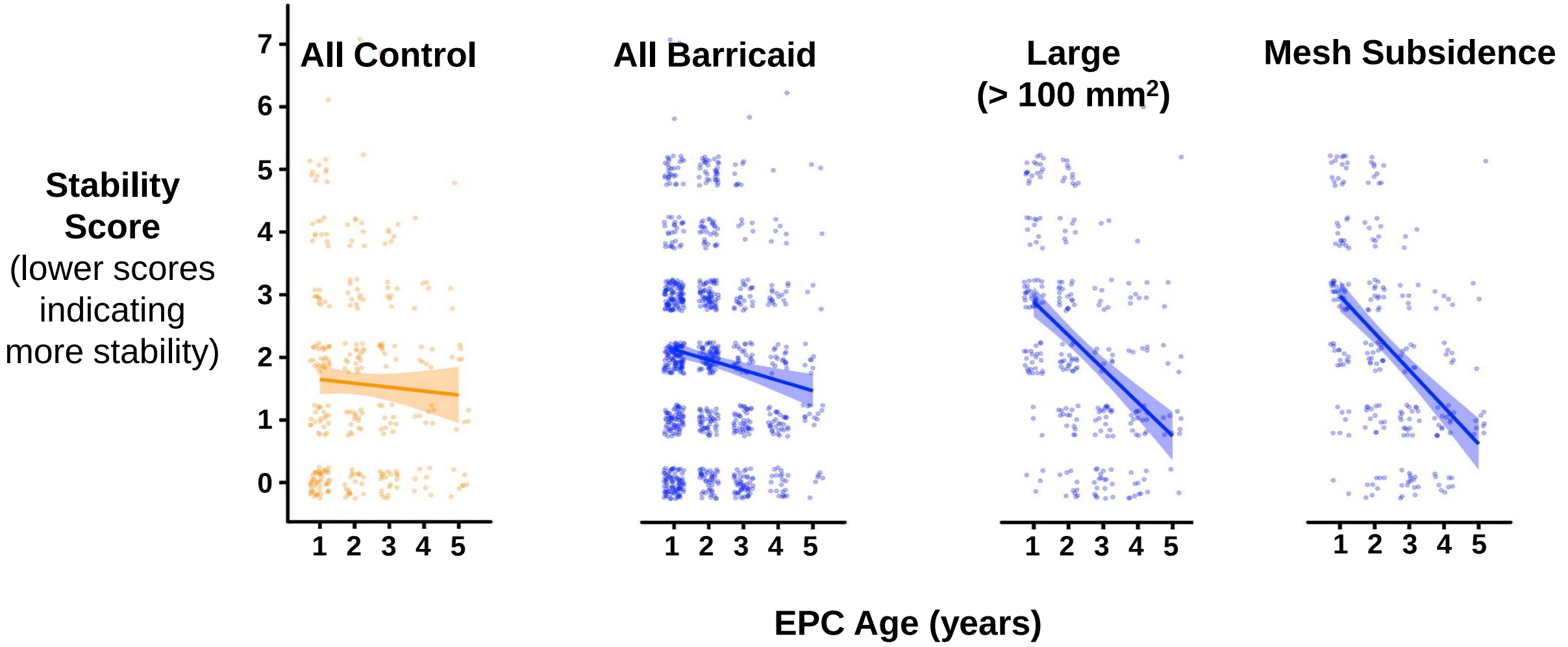


Qualitative Characteristics of EPCs Demonstrate Stability and Healing

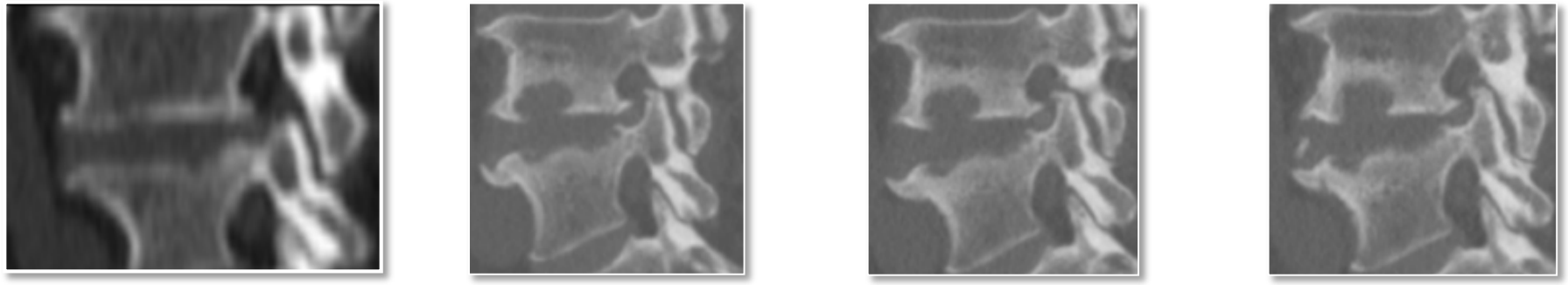
Intrinsic Stability Score: Higher Score = More Progressive

- **EPC growth rate**
  - Quantitative, % change in EPC size/year based on CT imaging
  - Not expected after discectomy
  - Suggests EPC has not yet started to stabilize
- **Presence of reactive edema surrounding EPC (MRI)**
  - Suggests association with active, ongoing degenerative process
- **Absence of a sclerotic margin (CT)**
  - Suggests EPC has not yet started healing process

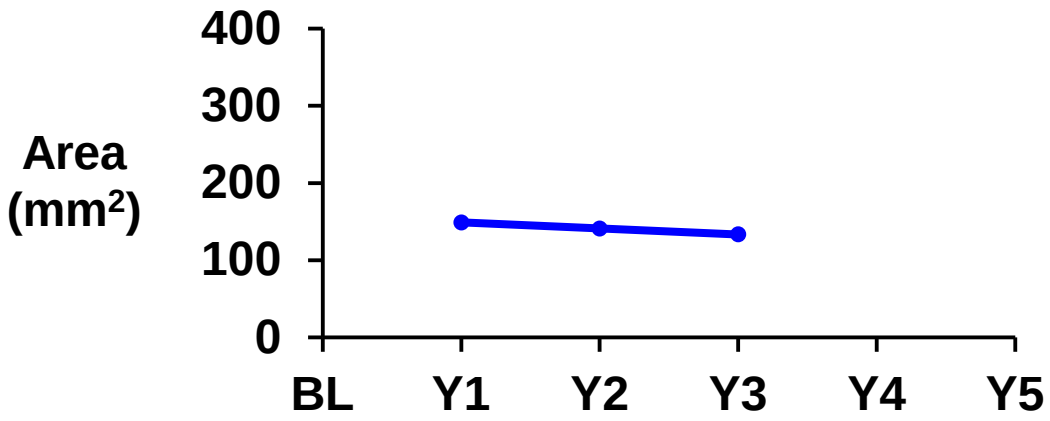
EPC Stabilize Over Time



Patient Example 1: Control



EPC Size

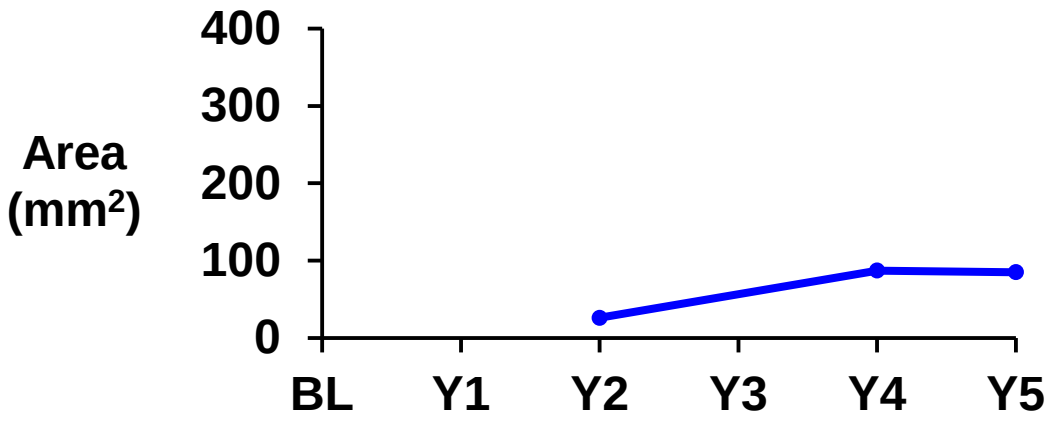


Clinical

	Pre	1Y	2Y	3Y	4Y	5Y
VAS Leg	100	0	0	0	-	-
VAS Back	0	0	0	0	-	-
ODI	64	0	18	0	-	-
SSI	Reoperation for reherniation 3 days post-op.					
Dev/Pro SAE	3 Total SAEs					

Patient Example 2: Barricaid

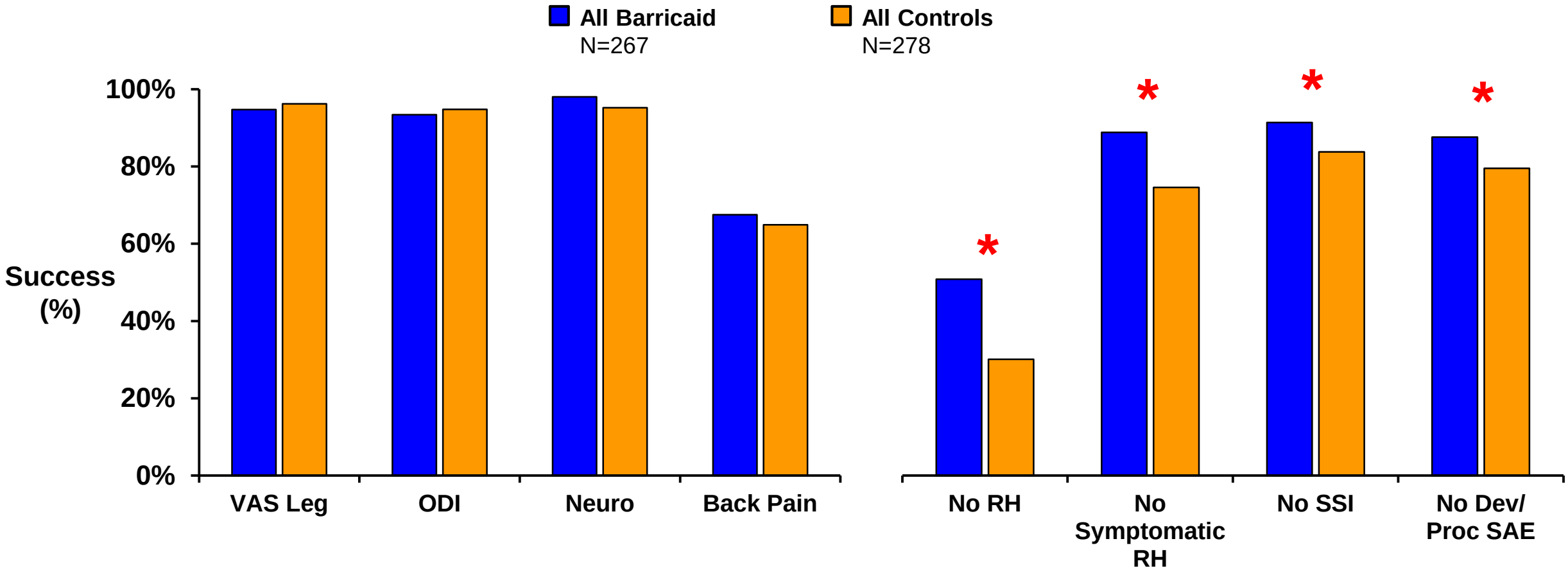
EPC Size



Clinical

	Pre	1Y	2Y	3Y	4Y	5Y
VAS Leg	96	5	1	-	3	1
VAS Back	4	7	1	-	2	1
ODI	75.6	24	10	-	0	0
SSI	None					
Dev/Pro SAE	None					

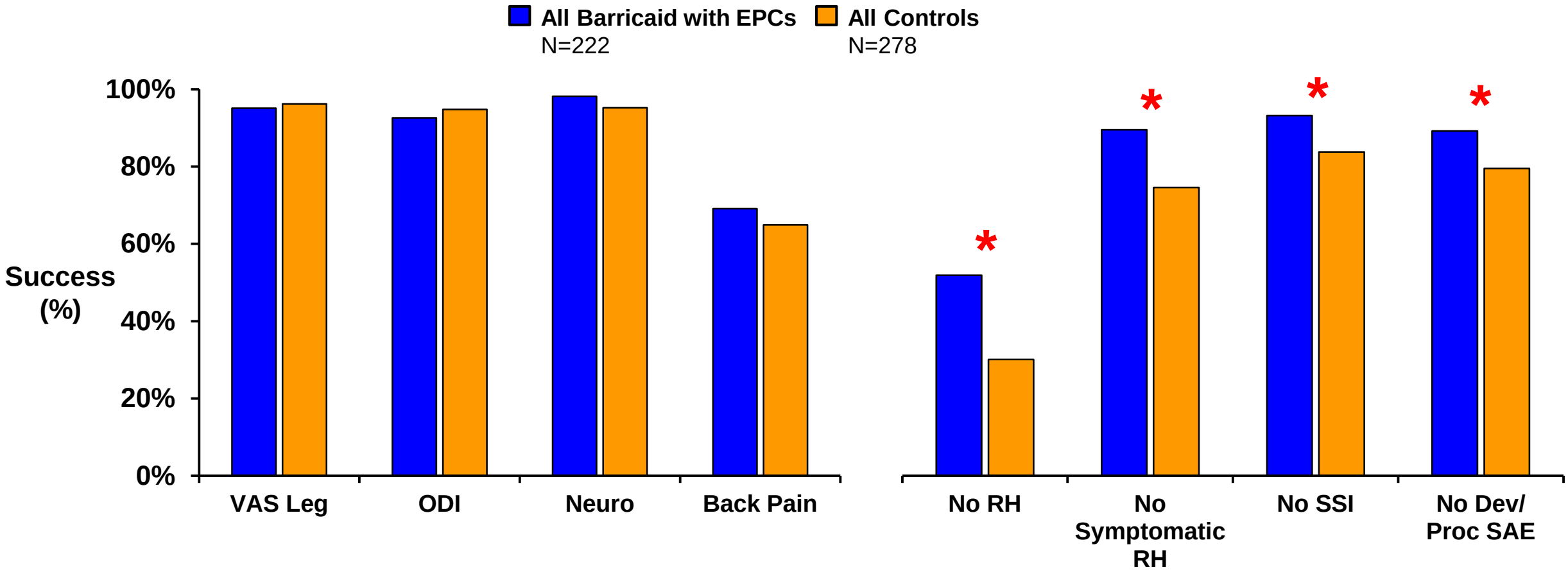
Clinical Outcomes at Year 2: All Barricaid vs. All Control



Barricaid Superior to Control

* Statistically significant difference

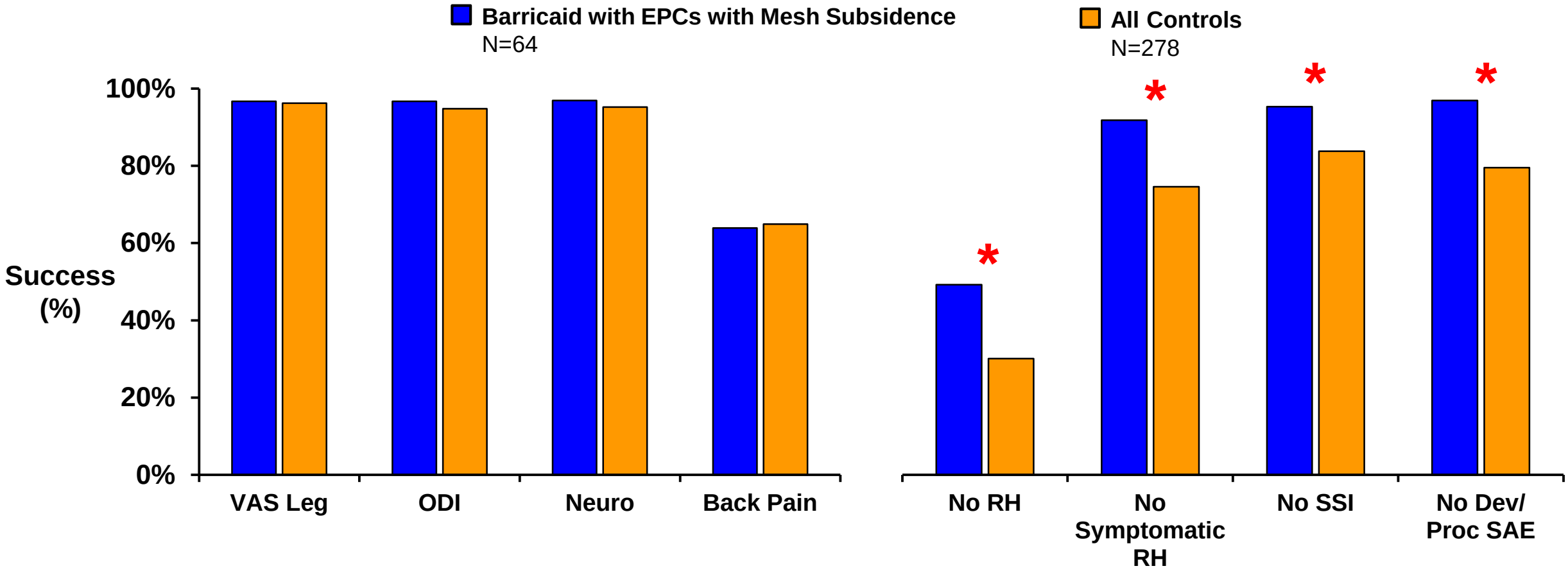
Clinical Outcomes at Year 2: Barricaid with EPCs vs. All Control



No Observed Clinical Impact of EPCs

* Statistically significant difference

Clinical Outcomes at Year 2: Barricaid With Mesh Subsidence vs All Control



No Observed Clinical Impact of EPCs with Mesh Subsidence

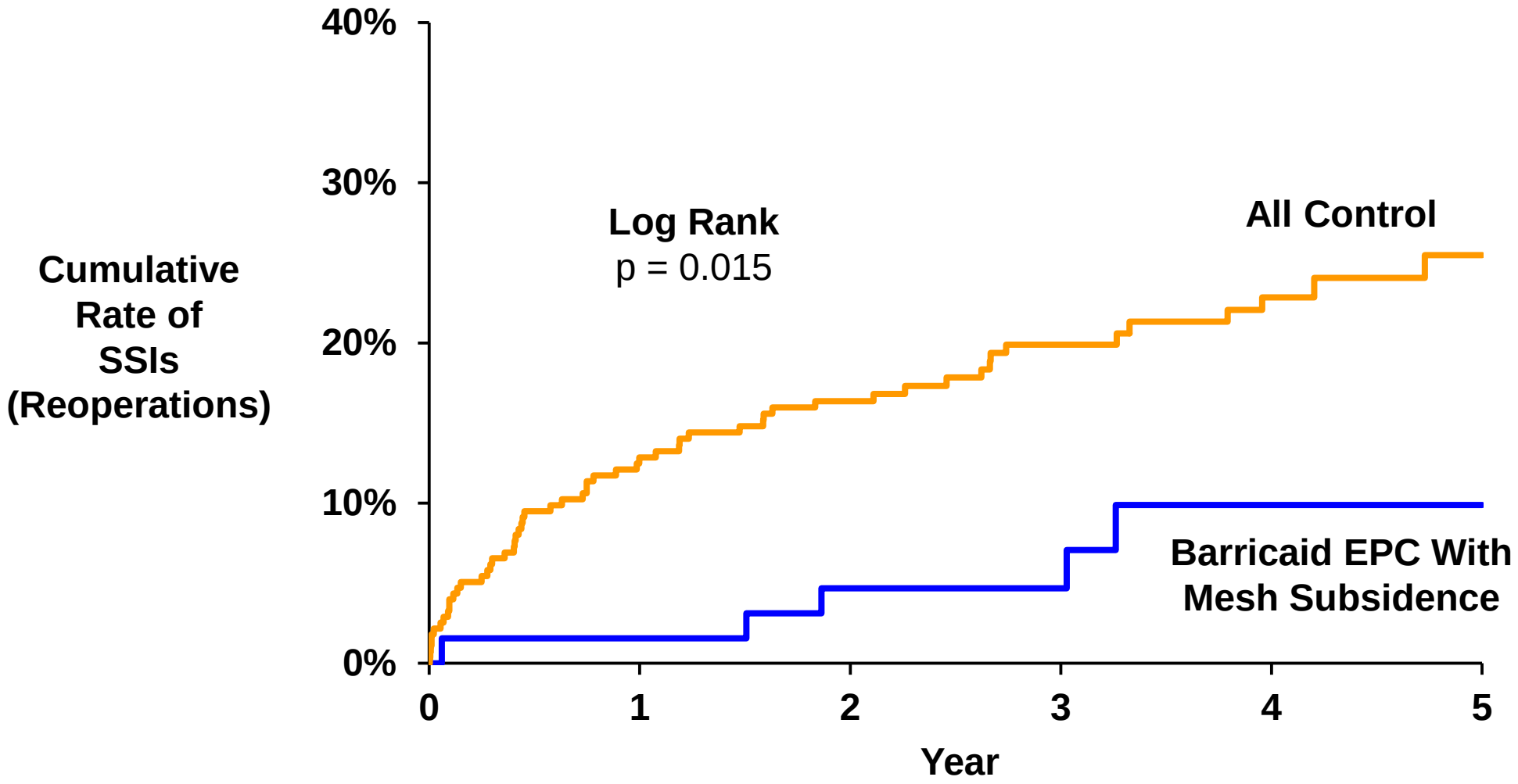
* Statistically significant difference

No Negative Effect on Clinical Outcomes

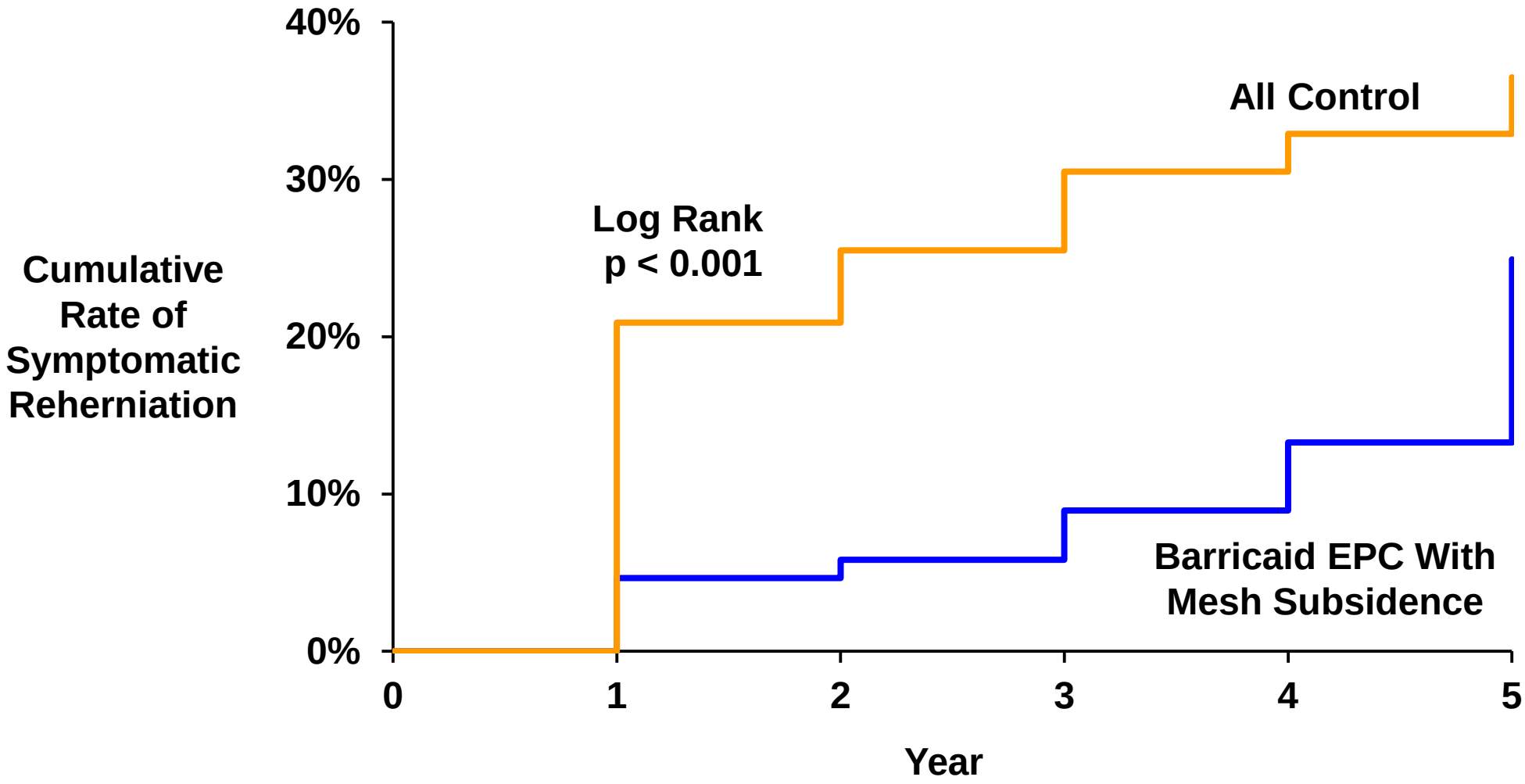
- No demonstrated negative effects of EPC in Barricaid patients on:
  - Symptomatic reherniation prevention
  - SSI prevention
  - Device integrity
  - Rate of related SAEs
  - Neurologic outcomes
  - Pain and function outcomes
- No significant correlations with EPCs and clinical outcomes using sophisticated models
  - Cox regressions of survival
  - Multivariate logistic regressions
  - Survival analyses

Long Term Data

EPC With Mesh Subsidence: Long-Term Safety (SSIs)



EPC With Mesh Subsidence: Long-Term Effectiveness (Reherniation)



Theoretical Risk of EPCs Not Supported by Data

- EPCs plateau in size over time
- Largest EPCs are same size with or without Barricaid
- Regardless of size, EPCs in Barricaid are not correlated with negative clinical outcomes or safety issues
- EPCs have no effect on the prevention of reherniation, reoperation and related SAEs
  - Barricaid benefits maintained over standard of care

Barricaid Benefit-Risk

Matthew McGirt, MD

Director Quality & Value Based Care Programs
Carolina Neurosurgery & Spine Associates

Associate Professor of Neurosurgery
University of North Carolina

Benefit-Risk: The Clinical Need

- Discectomy generally a successful surgery
- Recurrent disc herniation is an unsolved challenge
- Patients with large anular defects (≥ 6 mm) at greatest risk
  - 20%+ risk of reherniation and reoperation

Trial Patients, Technique, and Results are Generalizable to Broader Population

- Typical discectomy population and technique
- Control patients performed in line with reported literature
- Multi-center RCT evidence is best

Barricaid Benefits

- Superior on *a priori* co-primary endpoints at 2 years
- Pain and function benefits of discectomy maintained
- Statistically significant differences at 2 years:
  - Symptomatic reherniations reduced 56%
  - Secondary surgeries reduced 49%
  - Related SAEs reduced 33%
- Treatment effects durable to 5 years

Observed and Theoretical Risks of Barricaid

Device integrity observations

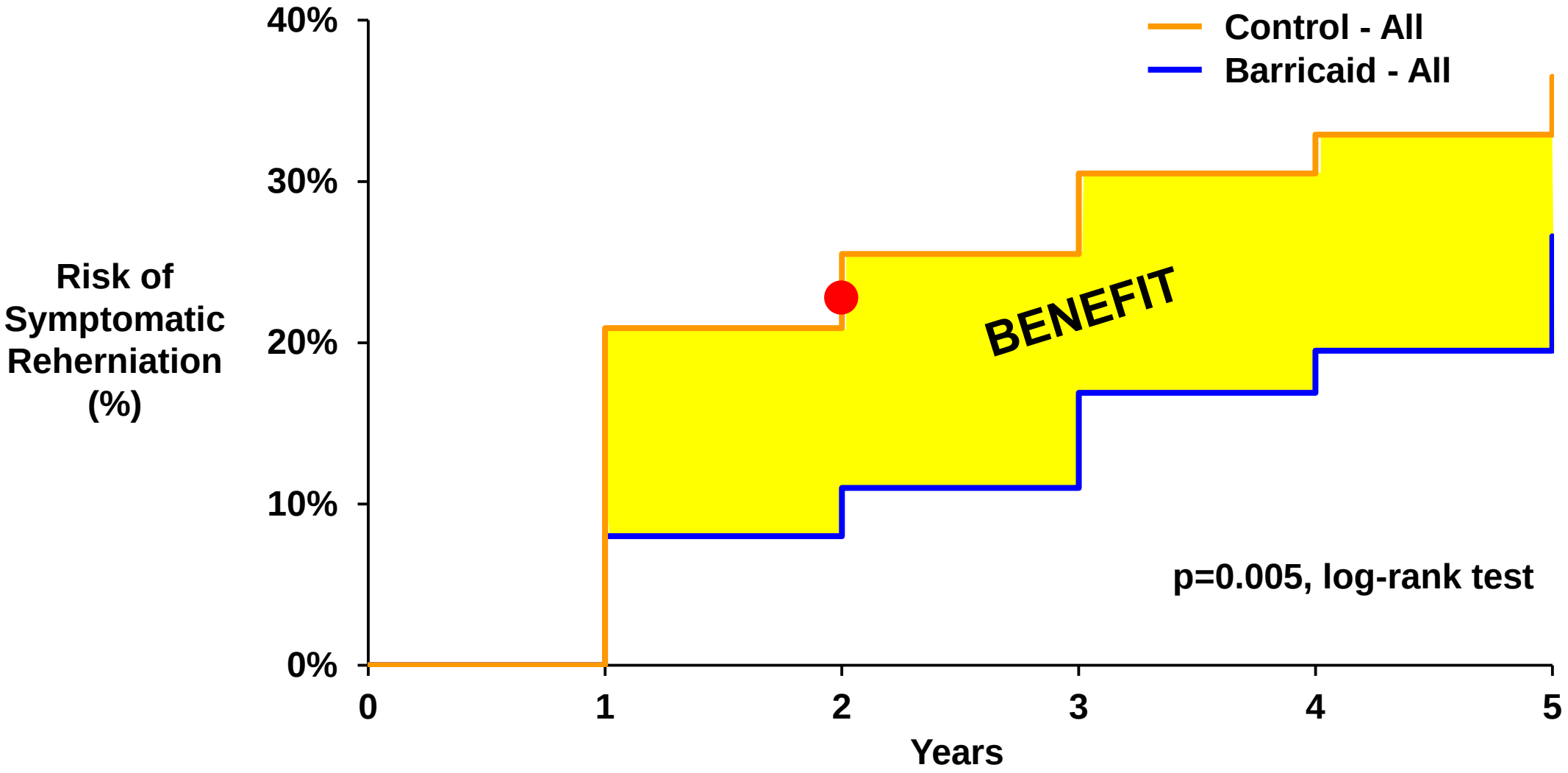
- n=21 (44%) asymptomatic
- n=19 (40%) observed with symptomatic reherniations
- n=8 (3%) stand-alone symptomatic device integrity issues

Theoretical EPC risk

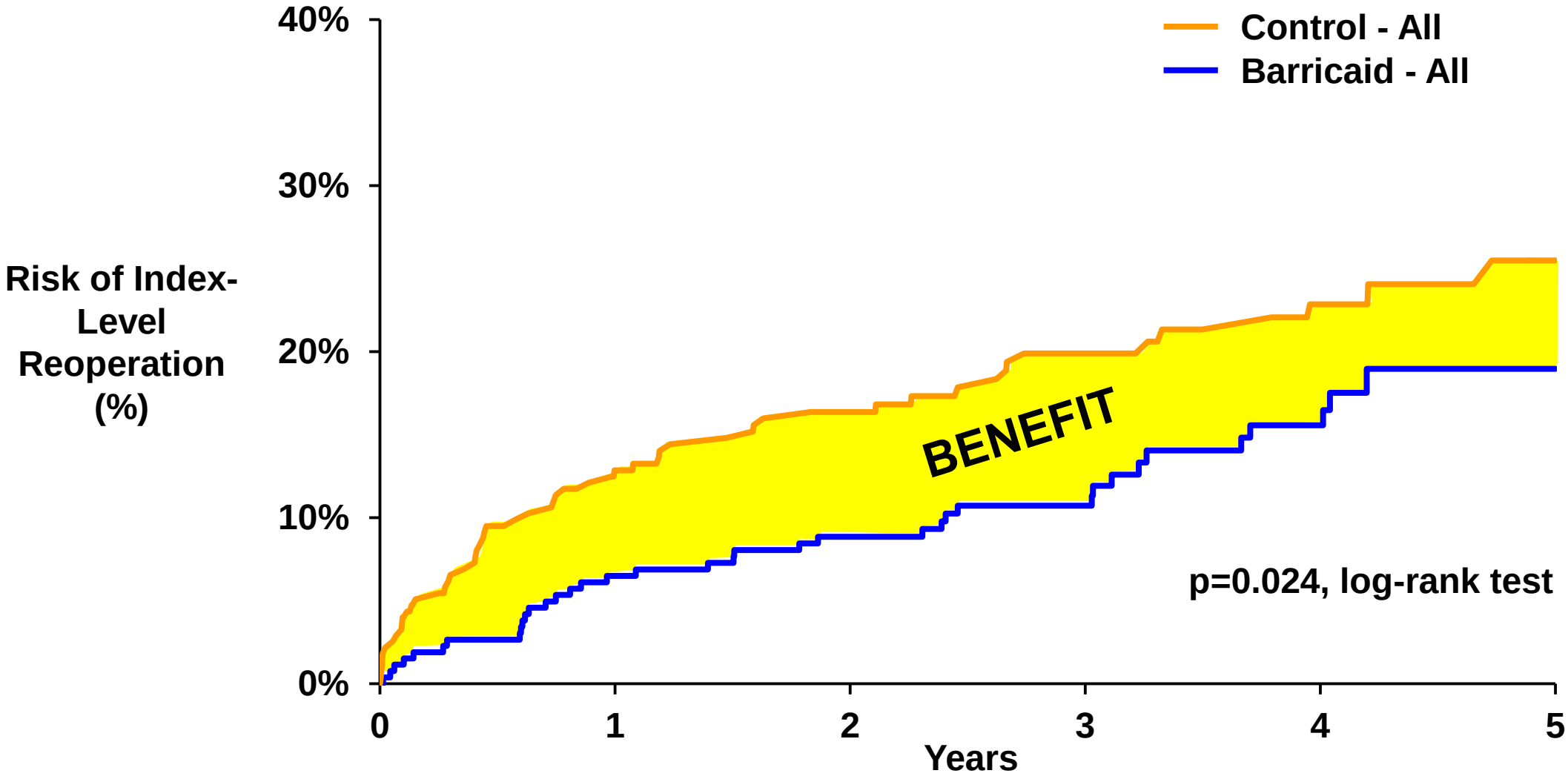
- No correlation with clinical outcomes
- EPCs stabilize
- Size < 8% of vertebral body
- Regardless of definition of “EPC”, “EPL” or “lytic”

Risks Outweighed By Decrease In Symptomatic Reherniations and Reoperations

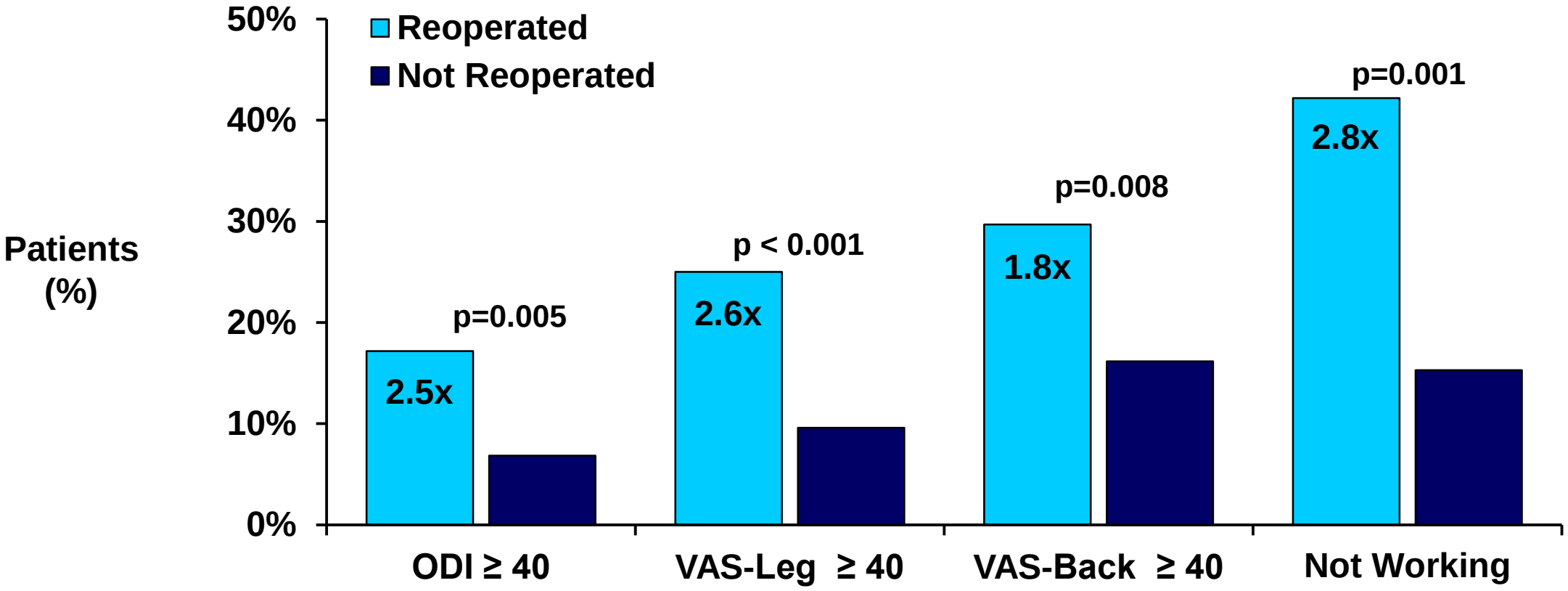
Reduction in Symptomatic Reherniations



Reduction in Secondary Surgical Interventions (Reoperations)

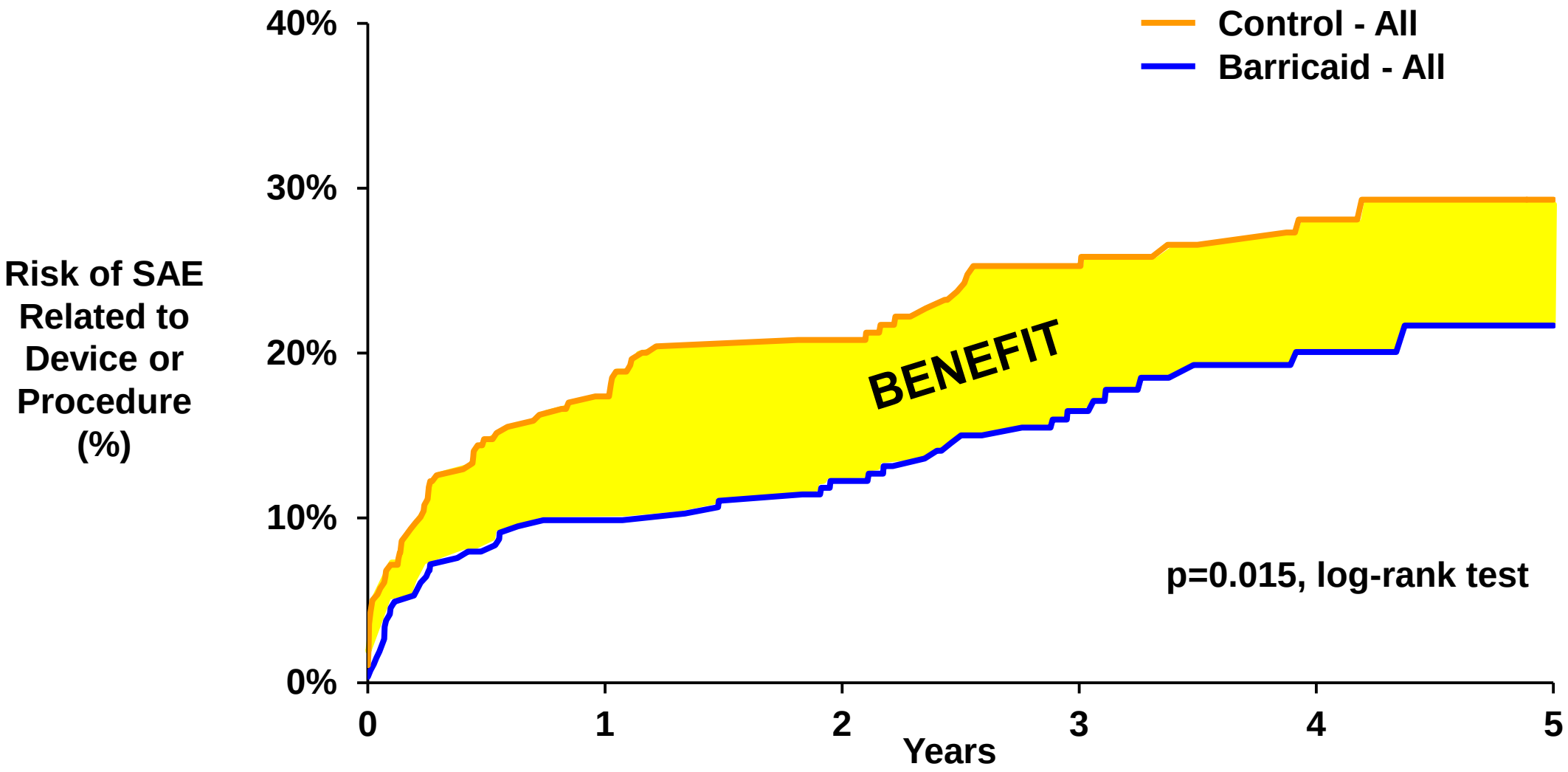


Significant Disability After Reoperation



Reoperated Patients Report More Chronic Pain and Disability than Non-Reoperated Patients at 2 Years

Reduction in Related Serious Adverse Events



Positive Benefit-Risk Profile for Barricaid

Patients with large defects at greater risk for

- Symptomatic RH (25.4%)
- SSIs (16.2%)
- Related SAEs (20.5%)

Barricaid significantly reduces

- Symptomatic RH (11.2%)
- SSIs (8.6%)
- Related SAEs (12.9%)

2-year Treatment Differential Maintained Through 5 Years

Observed and Theoretical Risks Outweighed by Significant Benefits

Backup Slides Shown

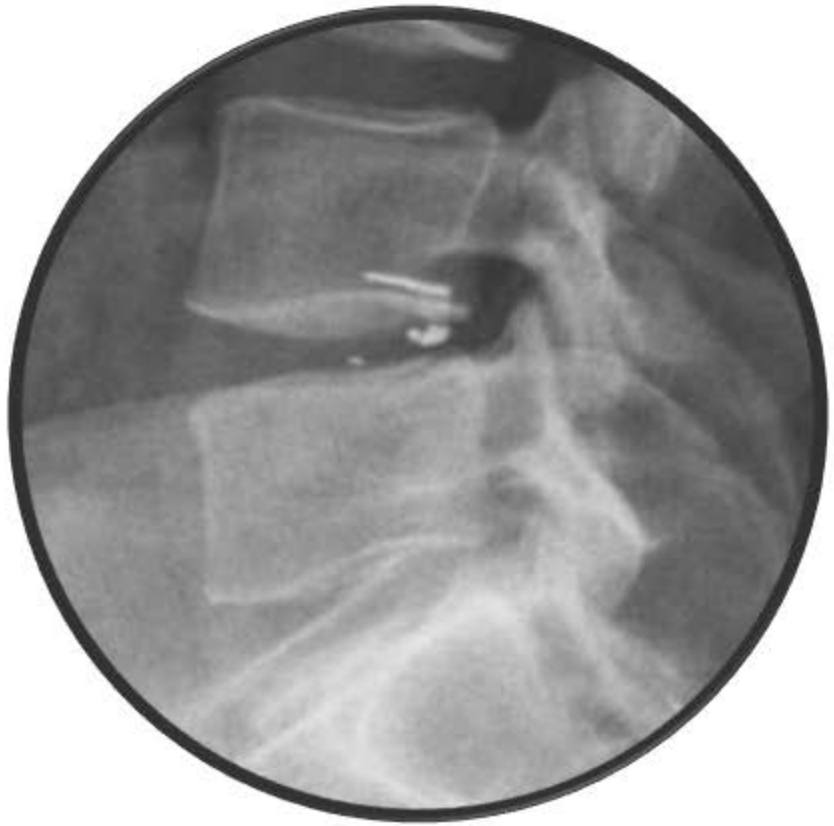
Effect of New Box Defects Created on Composite Score Components

Barricaid	New Defect & Box (n=73)	Others (n=199)	Chi-sq p-value
No Symptomatic Reherniations	89.4%	88.5%	0.846
No SSIs	91.8%	91.2%	0.888
No Related SAEs	87.7%	86.9%	0.872

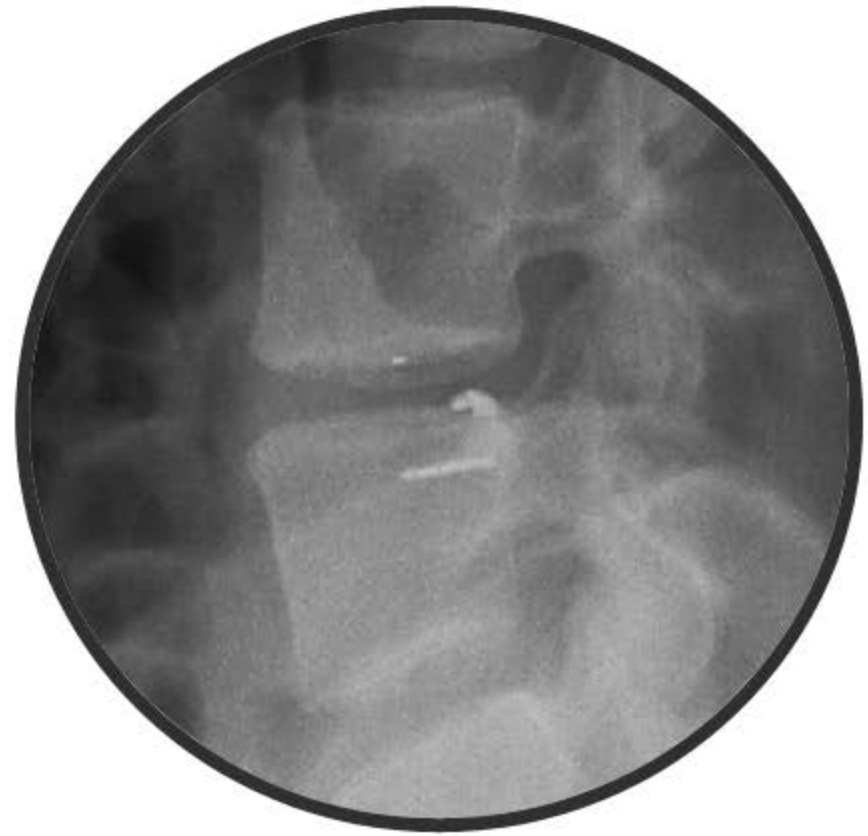
Control	New Defect & Box (n=76)	Others (n=202)	Chi-sq p-value
No Symptomatic Reherniations	79.2%	72.8%	0.295
No SSIs	85.5%	83.2%	0.634
No Related SAEs	84.2%	77.7%	0.232

Newly Created Box Defects Did Not Negatively Bias Results

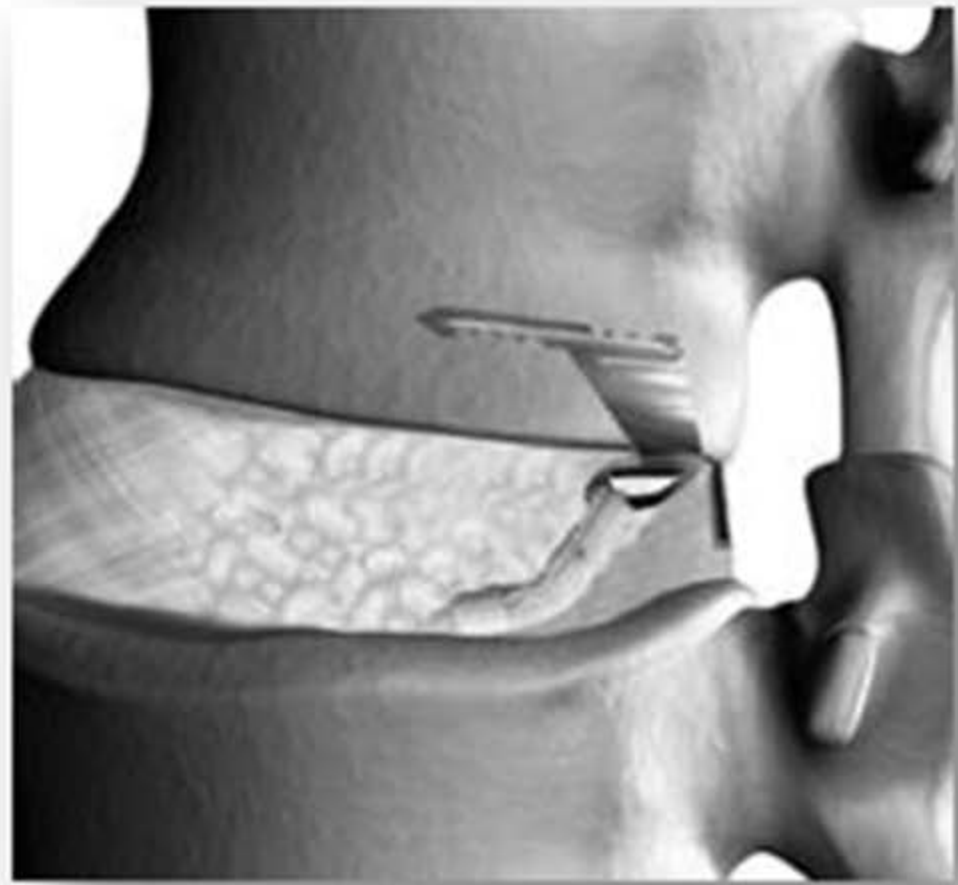
Ideal Barricaid Placement



Superior vertebral body



Inferior vertebral body



Barricaid Defect Geometry

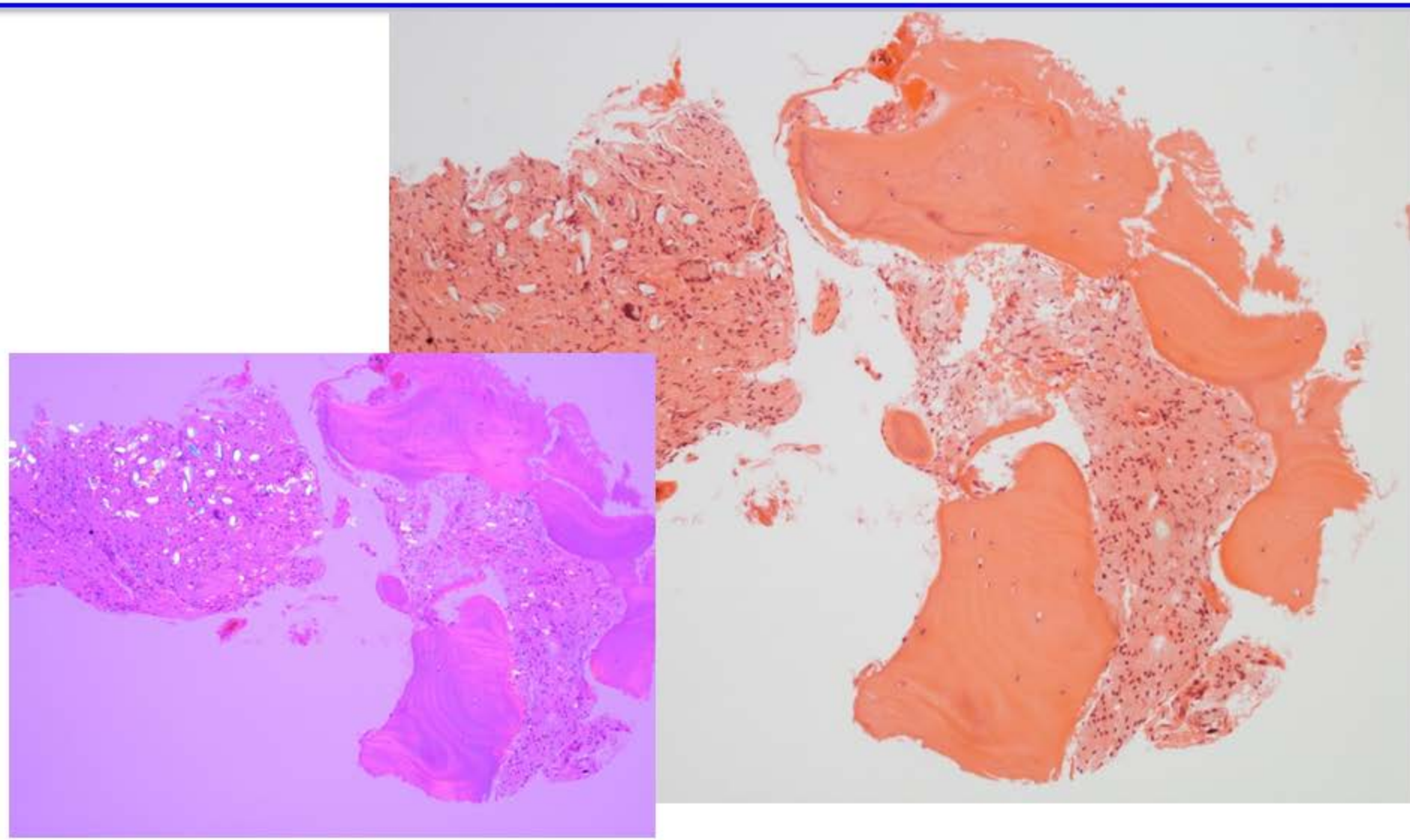
	Through existing defect	Created new defect	Total
Box	109 (40.1%)	73 (26.8%)	182
Other	67 (24.6%)	23 (8.5%)	90
Total	176	96	272

Barricaid EPCs by Endplate

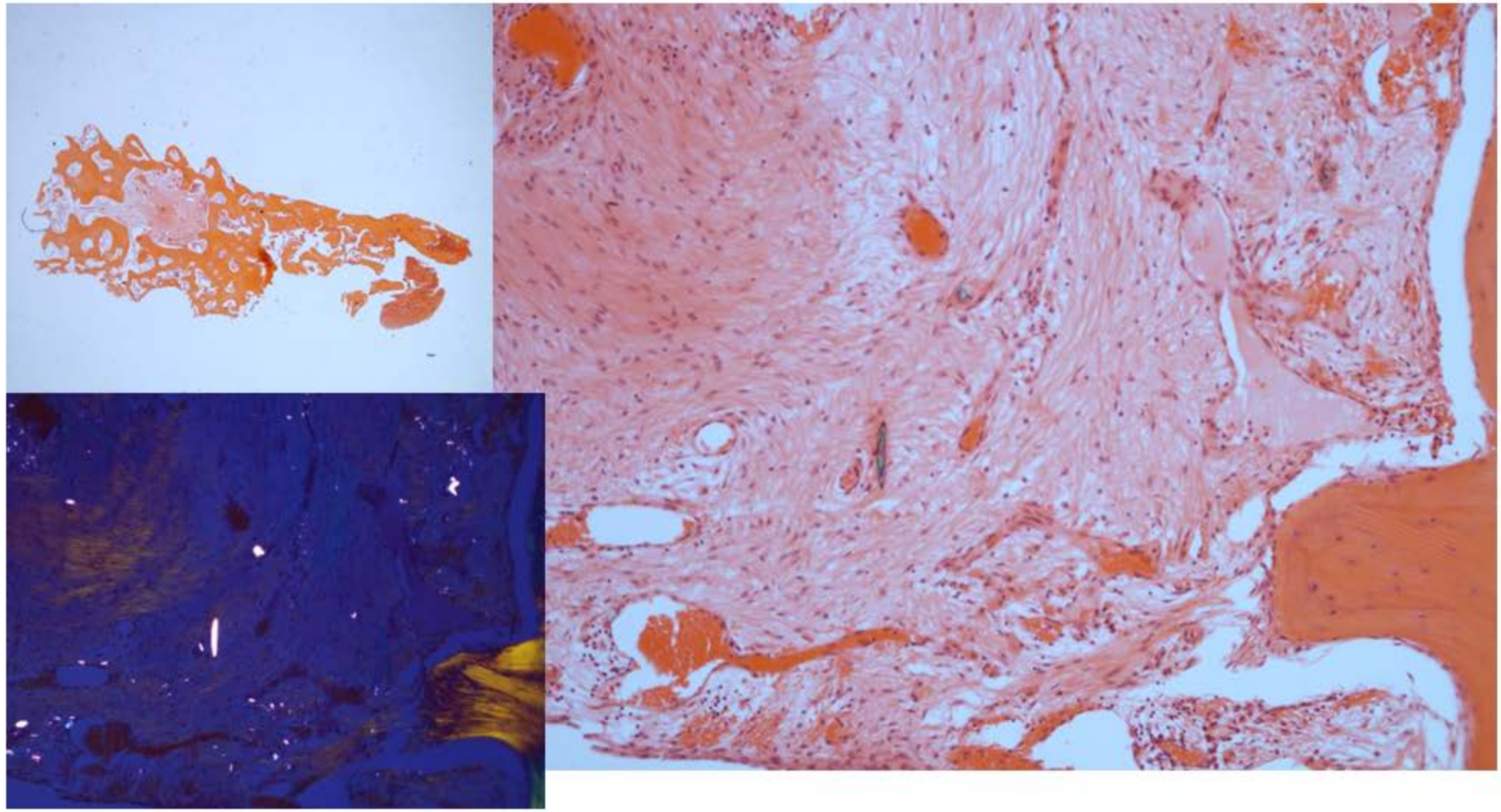
Device Orientation	Vertebral Body	Subjects	EPCs
Superior	Superior	74	107
	Inferior	74	84
Inferior	Superior	140	174
	Inferior	101	118

Device Orientation Superior: anchor implanted in Superior endplate
Device Orientation Inferior: anchor implanted in Inferior endplate

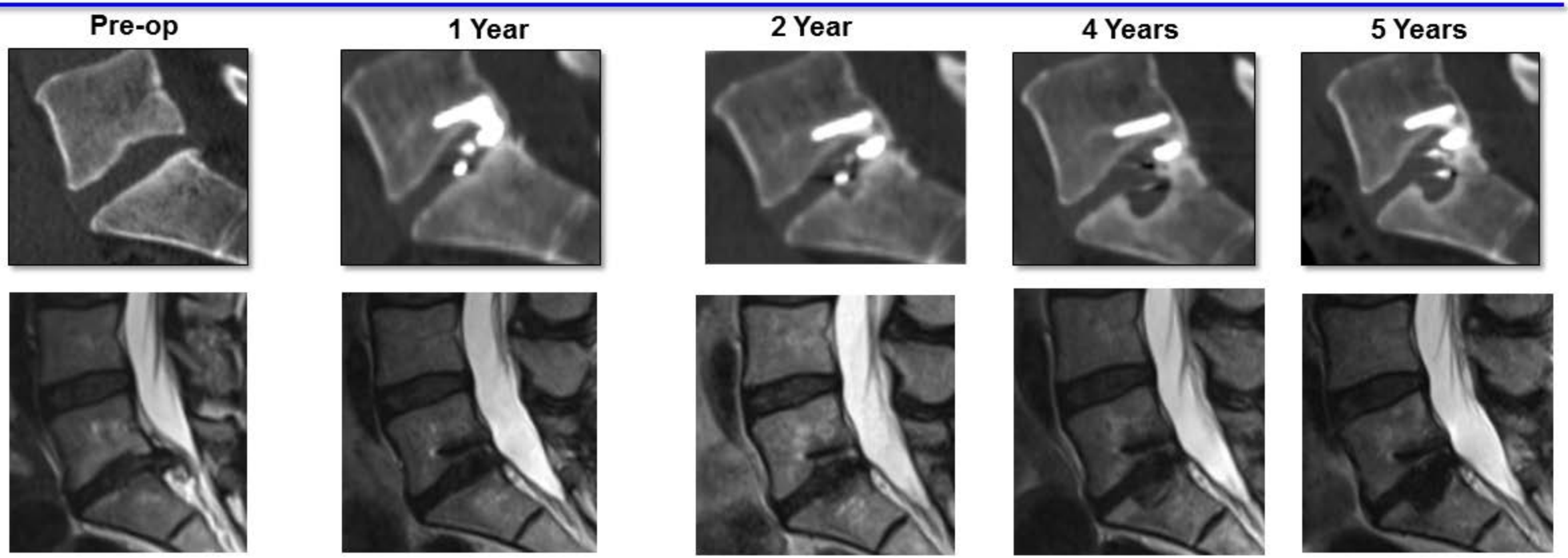
Retrieval Analysis: No Evidence of Active Osteolysis Associated with Particles



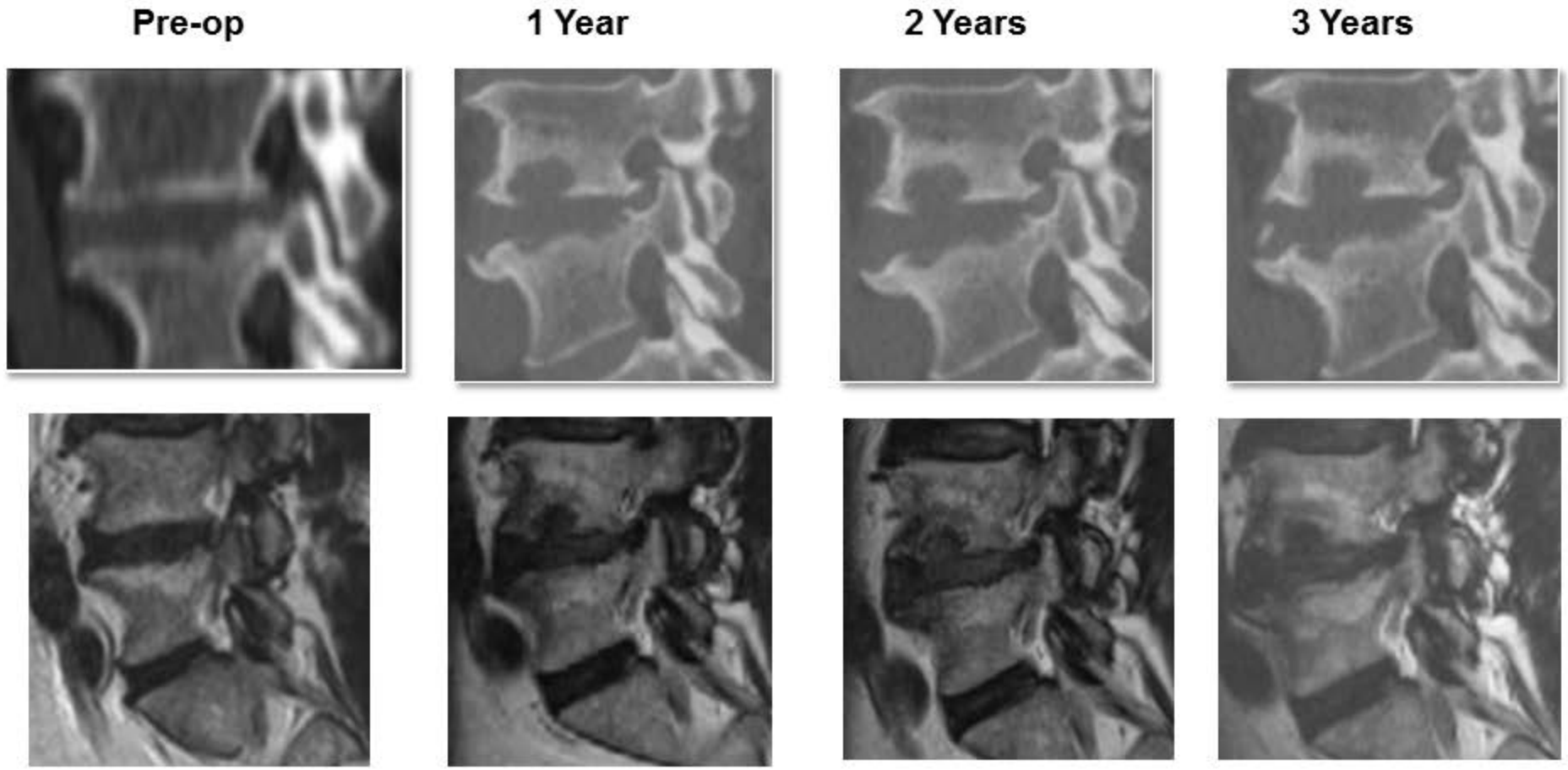
Retrieval Analysis: No Evidence of Active Osteolysis Associated with Particles



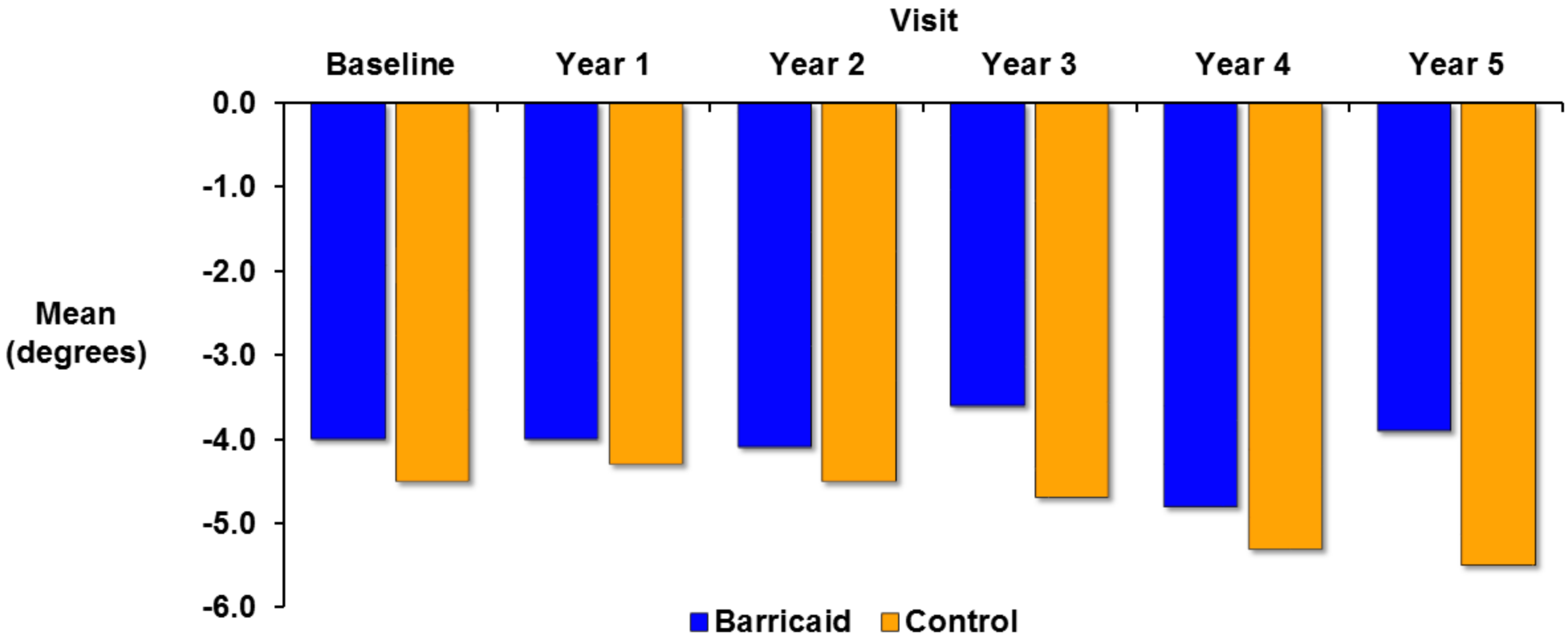
Patient Example 1, Pre-op – 5Y: Barricaid



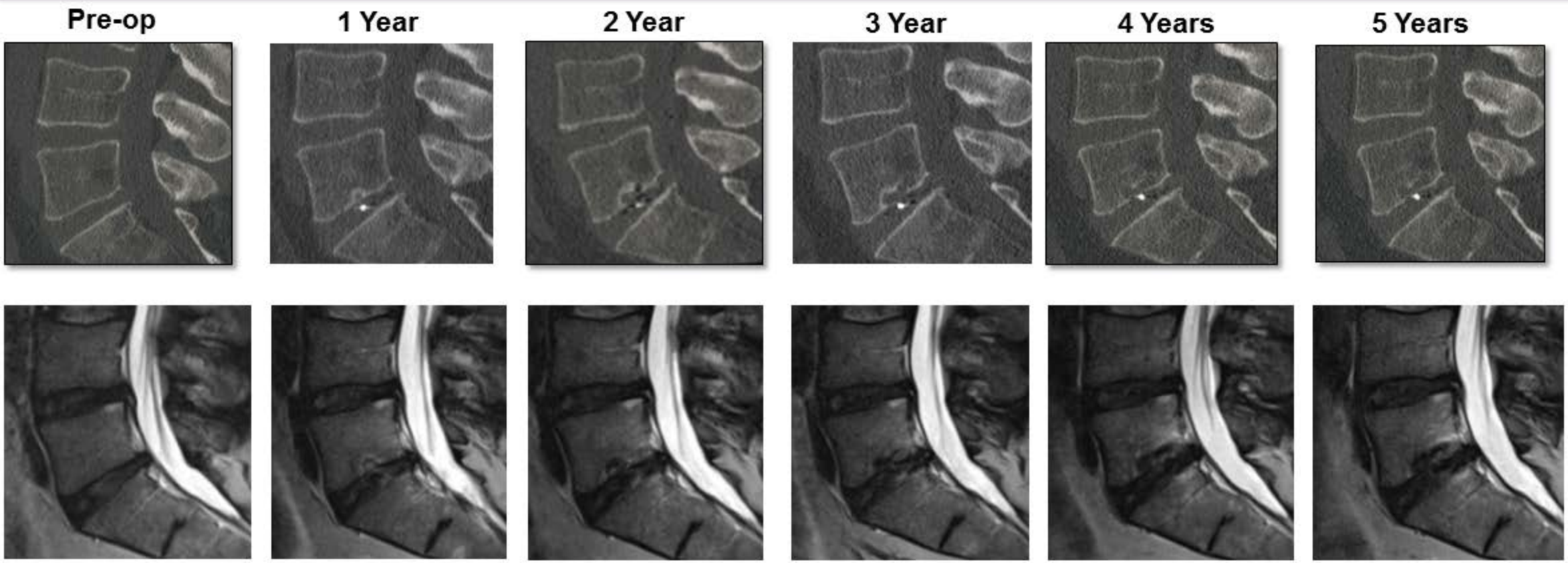
Patient Example 3: Pre-op – 5Y: Control



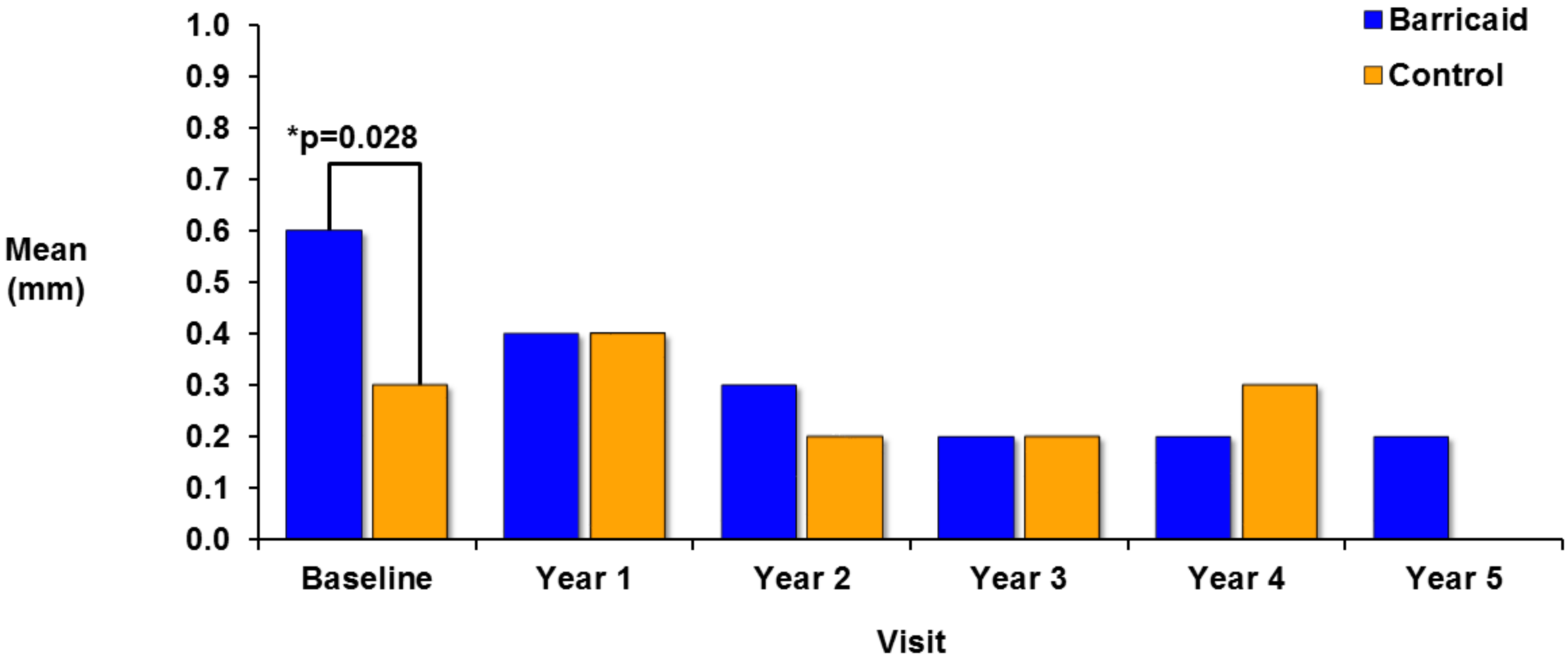
Rotation over Time (mITT)



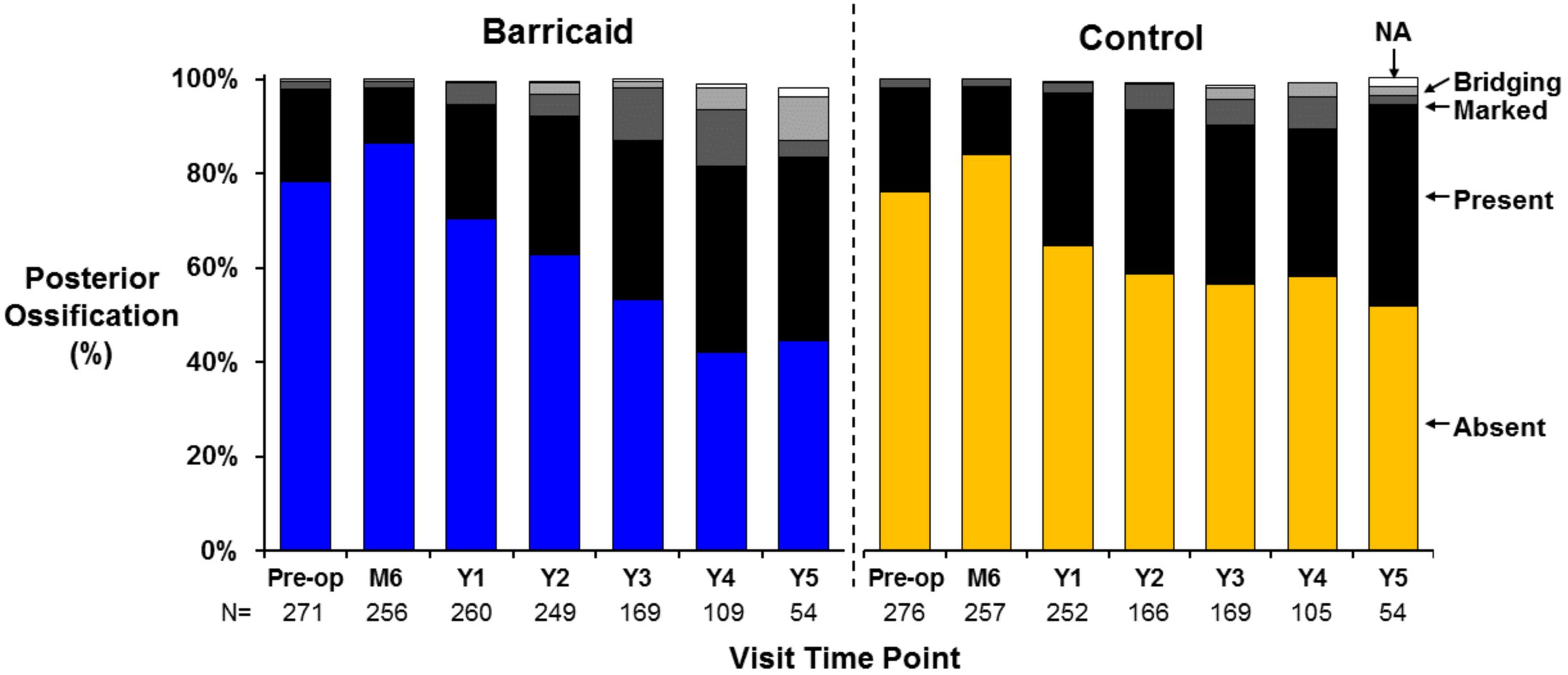
Patient Example 2, Pre-op – 5Y: Barricaid



Translation over Time (mITT)

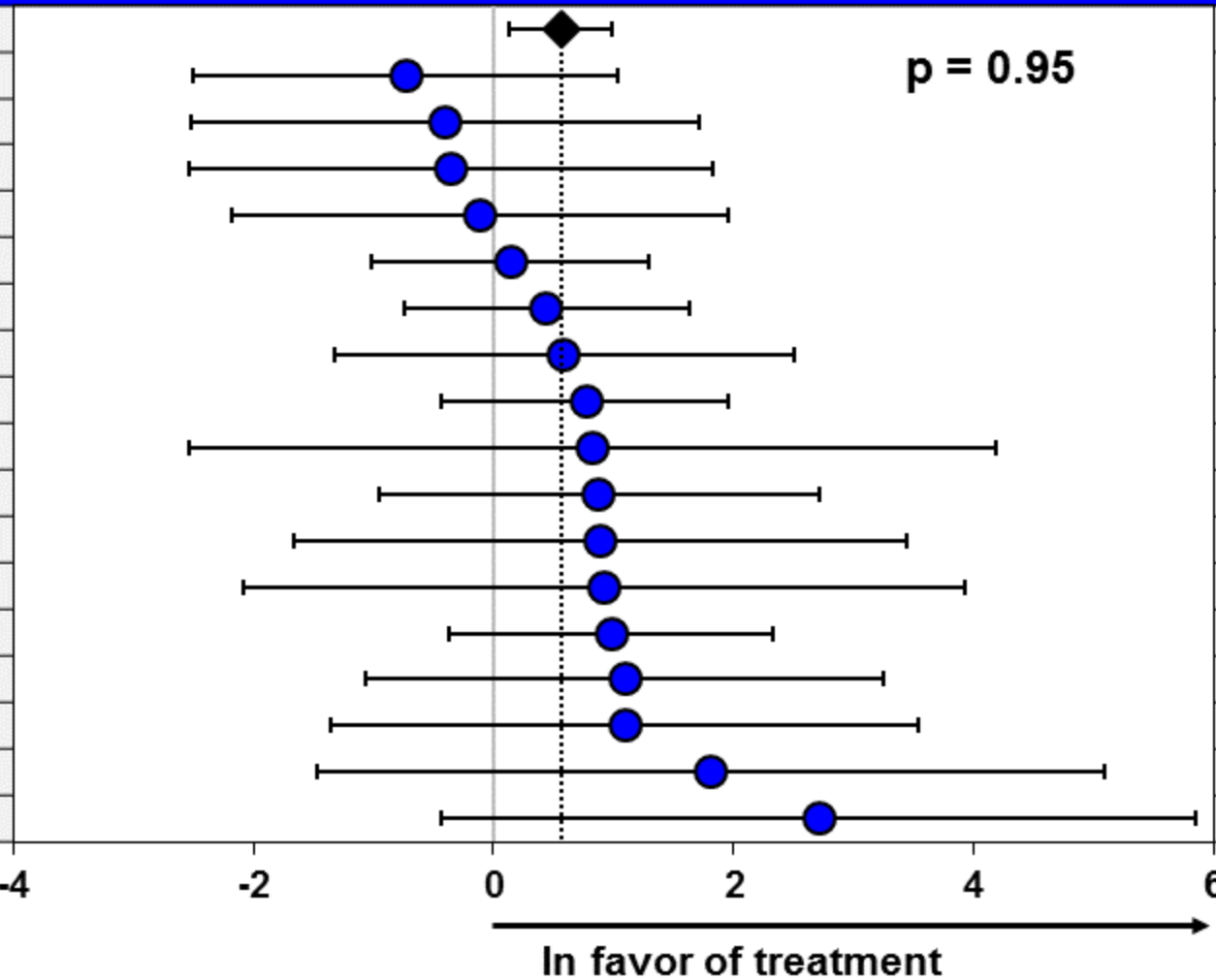


Qualitative Assessment of Posterior Ossification Barricaid and Control (mITT)

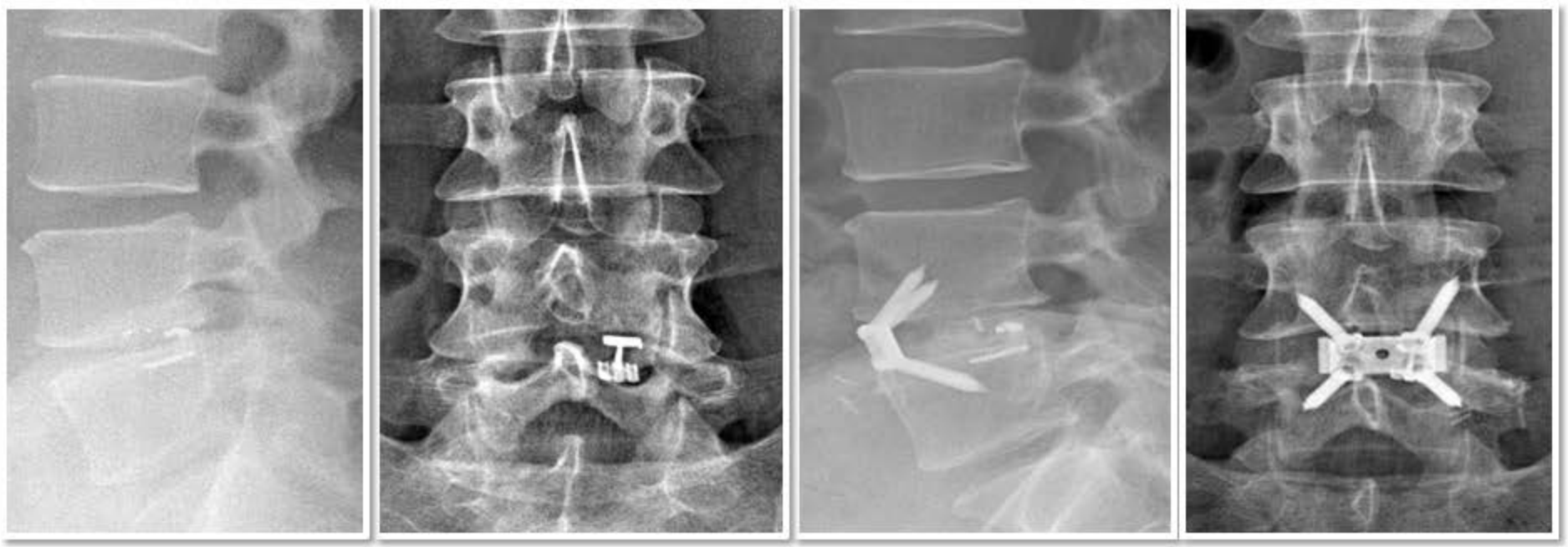


No Significant Site to Site Variability In Month 24 in Composite Endpoint Treatment Group Differences

Site	N	Primary Effectiveness % (95% CI)
FE Model	245	0.56% (0.13, 0.99)
11	17	-0.73% (-2.51, 1.04)
22	8	-0.41% (-2.52, 1.71)
10	12	-0.36% (-2.54, 1.83)
16	13	-0.12% (-2.18, 1.95)
28	27	0.15% (-1.01, 1.30)
12	22	0.44% (-0.75, 1.63)
19	14	0.59% (-1.33, 2.51)
17	27	0.77% (-0.43, 1.96)
99	9	0.83% (-2.53, 4.19)
20	19	0.88% (-0.95, 2.71)
23	11	0.89% (-1.66, 3.45)
26	5	0.92% (-2.09, 3.92)
13	28	0.98% (-0.37, 2.33)
14	7	1.10% (-1.06, 3.25)
18	12	1.10% (-1.35, 3.54)
21	6	1.81% (-1.47, 5.09)
15	8	2.71% (-0.44, 5.85)



ALIF



Age (< 43 years vs. ≥ 43 years) Affect on Composite Score Components

Barricaid	≥ 43 (n=149)	< 43 (n=123)	Chi-sq p-value
No Symptomatic Reherniations	93.9%	82.4%	0.005
No SSIs	93.8%	88.4%	0.117
No Related SAEs	91.3%	82.1%	0.025

Control	≥ 43 (n=147)	< 43 (n=131)	Chi-sq p-value
No Symptomatic Reherniations	74.6%	74.6%	0.995
No SSIs	83.7%	84.0%	0.947
No Related SAEs	77.6%	81.7%	0.395

Barricaid Clinical Performance Influenced by Fewer Symptomatic Reherniations in Older Patients

Effectiveness by Patient Sex Composite Primary Endpoint

Composite Primary Endpoint - Protocol	Female	Male
Barricaid	24.2%	30.1%
Control	18.8%	17.7%

Composite Primary Endpoint – Patient Centered	Female	Male
Barricaid	73.6%	77.6%
Control	52.0%	71.6%

Barricaid (N=116 Female / N=156 Male); Control (N=107 Female / N=171 Male

Pre-Market Bench Testing

- Cadaver Implantation Study
- Monotonic push-out testing (bone foam & UHMWPE)
- Cyclic push-out testing
- Cyclic nucleus pressure testing
- Cyclic compression-shear testing
- Monotonic nucleus pressure testing
- Monotonic compression-shear testing

Results Demonstrated Safety Under Extreme Physiological Pressures and Loads

Non-Clinical Testing to Recreate Detachment

- Detachment test developed to replicate the detachment behavior observed in the RCT
- Tension applied using 2 separate directions in accordance with clinically observed motions
  - Medial
  - Posterior
- Retrieval analysis of benchtop detachments
  - Similar to clinical explants
  - Mechanically-mediated, not degradation

Medial

Learning Curve (1st 4 patients vs. Remainder) Affect on Composite Score Components

Barricaid	1st 4 Subj (n=76)	~1st 4 Subj (n=196)	Chi-sq p-value
No Symptomatic Reherniations	87.5%	89.2%	0.712
No SSIs	89.3%	92.2%	0.455
No Related SAEs	84.2%	88.3%	0.370

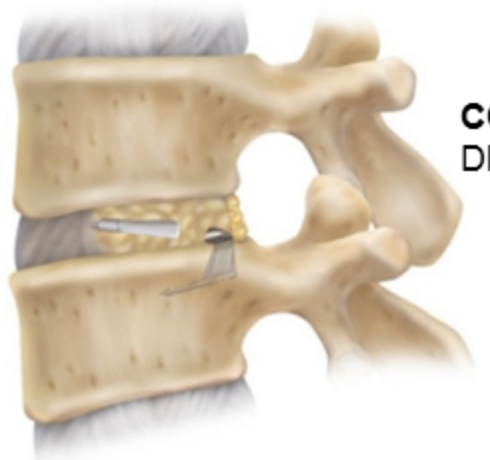
Control	1st 4 Subj (n=72)	~1st 4 Subj (n=206)	Chi-sq p-value
No Symptomatic Reherniations	77.8%	73.6%	0.506
No SSIs	84.7%	83.5%	0.808
No Related SAEs	73.6%	81.6%	0.151

Clinical Data Demonstrates that Learning Curve Has No Effect On Barricaid Clinical Performance

Device Integrity Endpoint Definition

Device Condition Failure

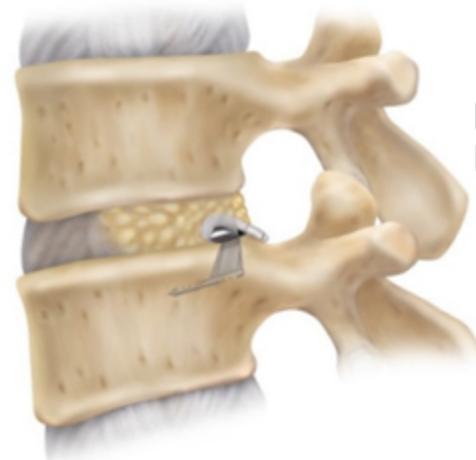
- Fracture of anchor component
- Disassembly of occlusion component



CONDITION:
DISASSEMBLED

Device Migration

- Motion ≥ 2 mm of anchor
- Migration of occlusion component into epidural space



MIGRATION:
PRESENT

“Stand alone” symptomatic device integrity patients

- 8 patients identified as “ stand alone“ symptomatic device integrity patients – all “failures” of the composite
  - 3 SAE: Mesh migration + SAE
  - 3 SSI: 2 Mesh migration/detachment and removal, 1 Anchor migration and removal
  - 1 Neurologic deterioration **preceding** mesh migration
  - 1 Mesh migration and never achieved MCID for ODI
- 3/8 re-operated

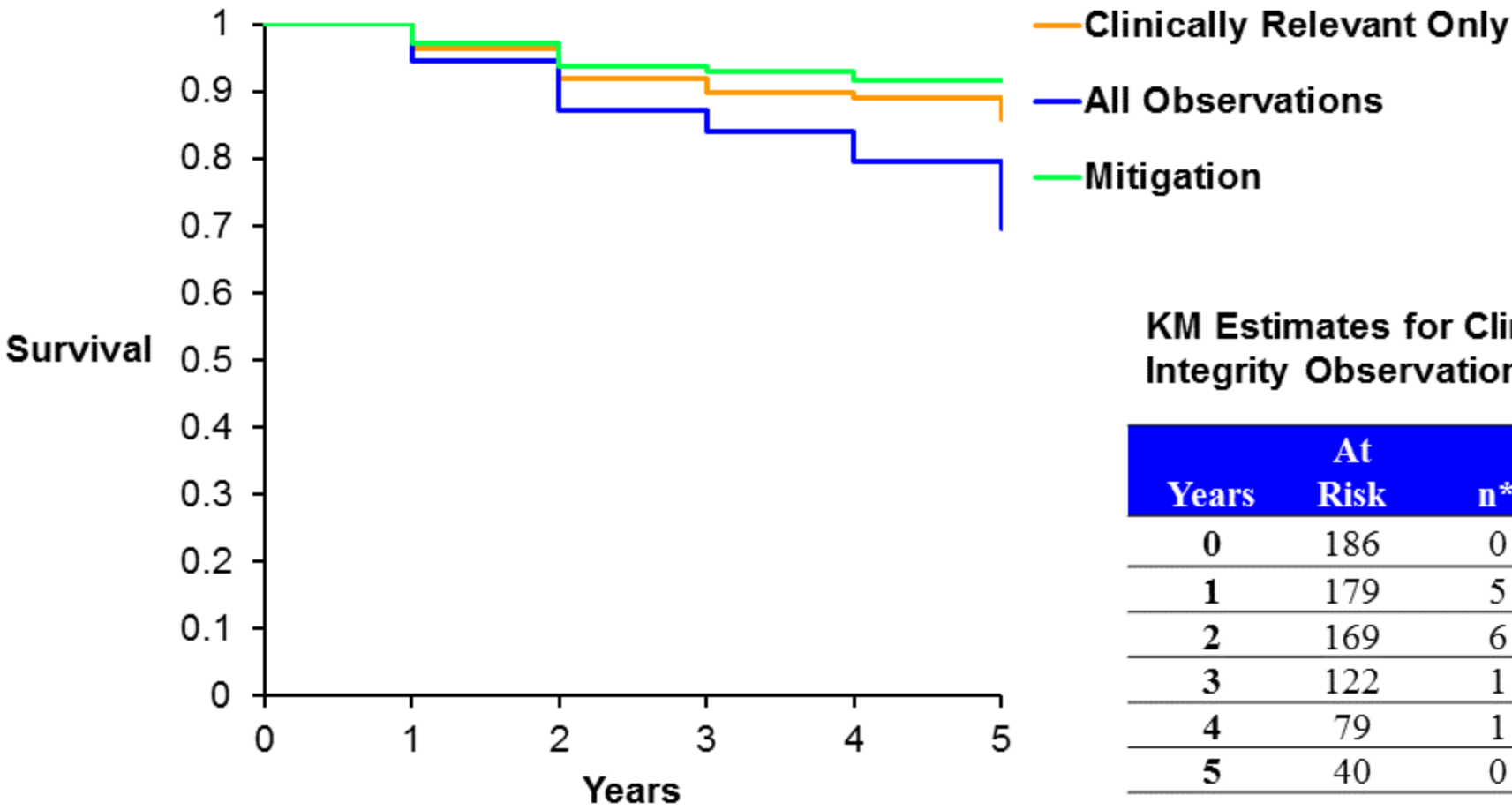
Potential Mitigation: Cox Regression Analysis

- Backward step-wise regression of 5-year clinically relevant device integrity with baseline and intra-operative characteristics
- Inclusion into final model if p<0.10

		p-value	Hazard Ratio	95% CI	
				LB	UB
Surgical	Implant size per IFU	0.001	7.692	2.222	26.316
Demographic	Preop disc height (quartiles)	0.022	1.544	1.065	2.238

- Implant size narrower than defect width:
  - Device integrity observation risk increased by 7.7x
- Each quartile increase in pre-operative disc height:
  - Device integrity observation risk increased by 1.5x

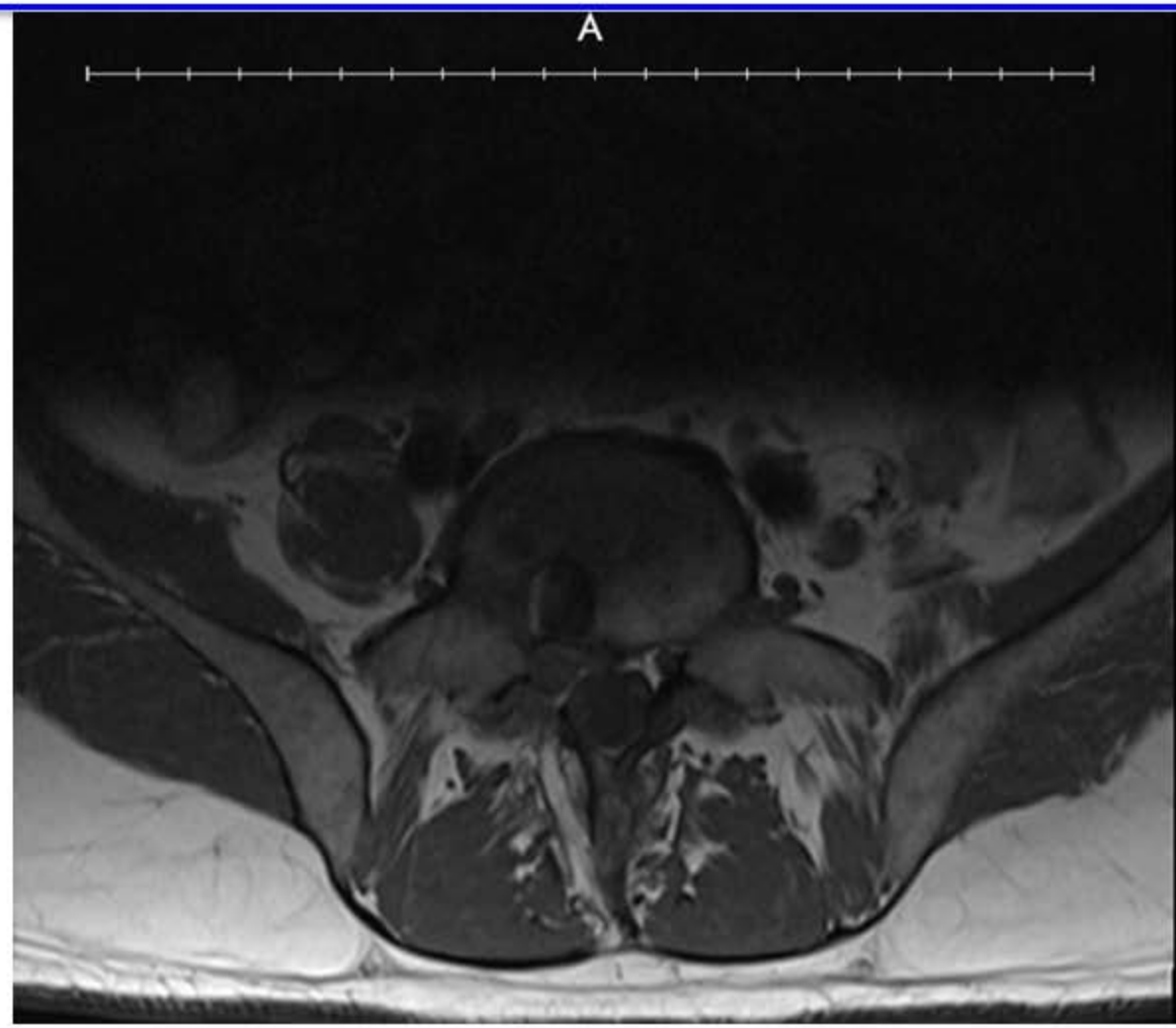
Mitigation Survival Approach to Device Integrity



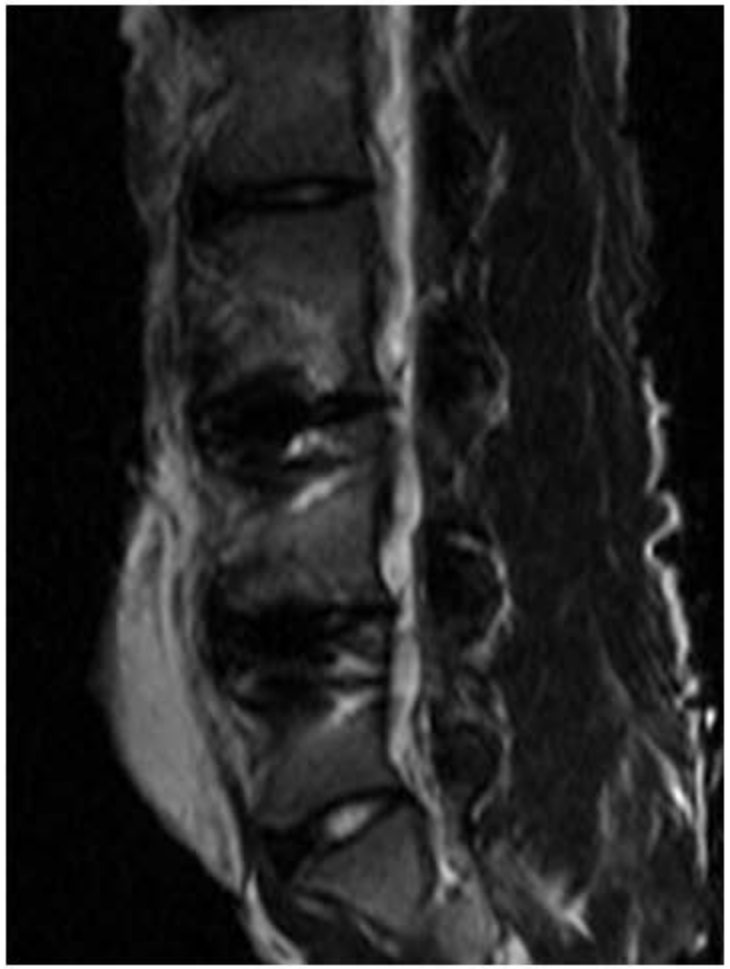
KM Estimates for Clinically Relevant Device Integrity Observations Excluding Mitigated Events

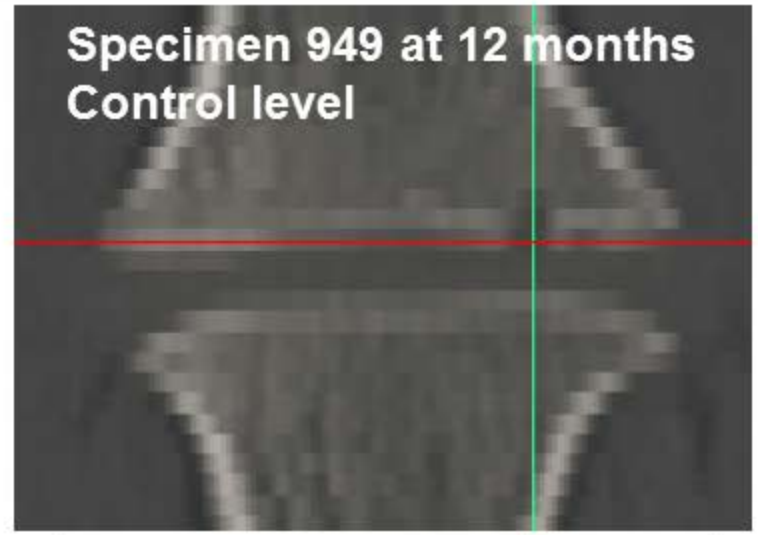
Years	At Risk	n*	%	95% CI LB	95% CI UB
0	186	0	0.00%		
1	179	5	2.79%	1.17%	6.58%
2	169	6	6.24%	3.51%	10.99%
3	122	1	7.01%	4.03%	12.06%
4	79	1	8.19%	4.74%	13.97%
5	40	0	8.19%	4.74%	13.97%

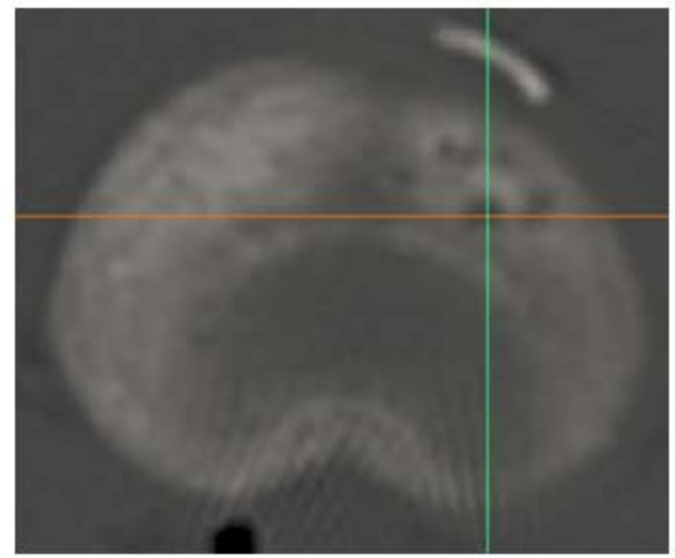
Barricaid Reherniation: Axial MRI (12 Months)



Baboon: 12 Month Sacrifice (Specimen 949)

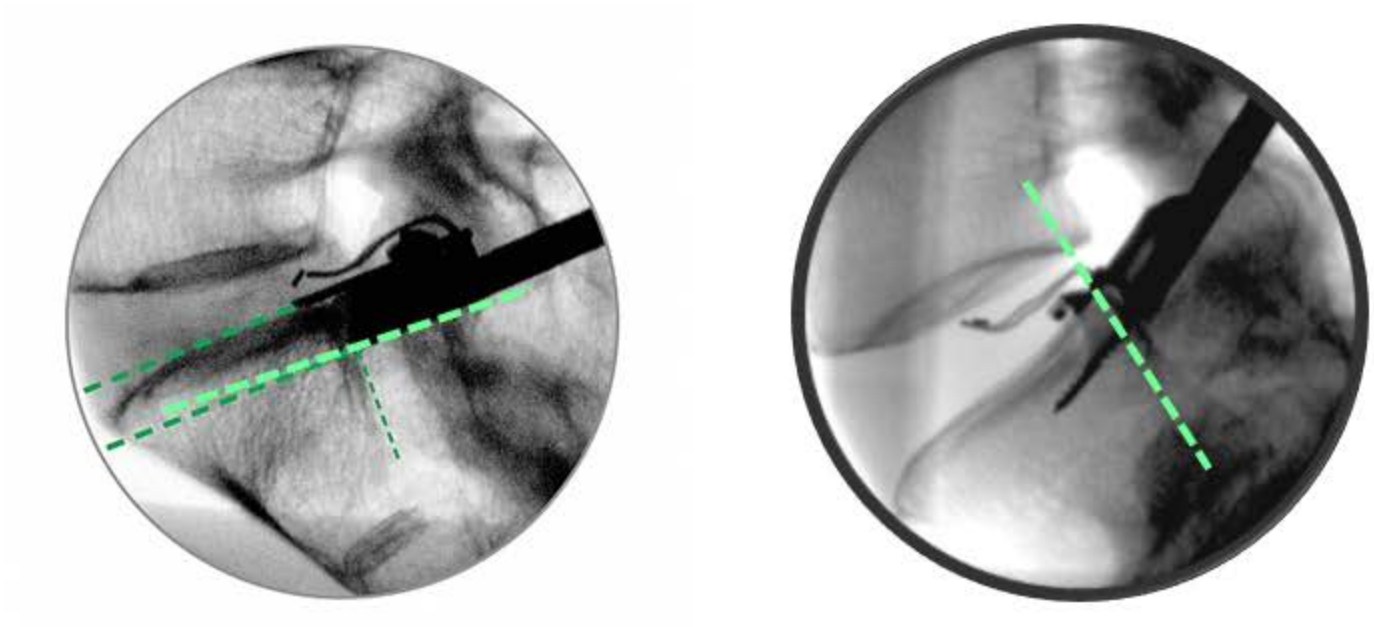






Anchor Placement

- Final position:
  - Parallel to endplate
  - 2mm countersunk



Defect Geometry Through Existing/ New Defect

	Barricaid (N=272)		Control (N=278)	
	Through existing defect	Created new defect	Through existing defect	Created new defect
Box	109 (40.1%)	73 (26.8%)	83 (29.9%)	76 (27.3%)
Other	67 (24.6%)	23 (8.5%)	86 (30.9%)	33 (11.9%)
Total	176	96	169	109

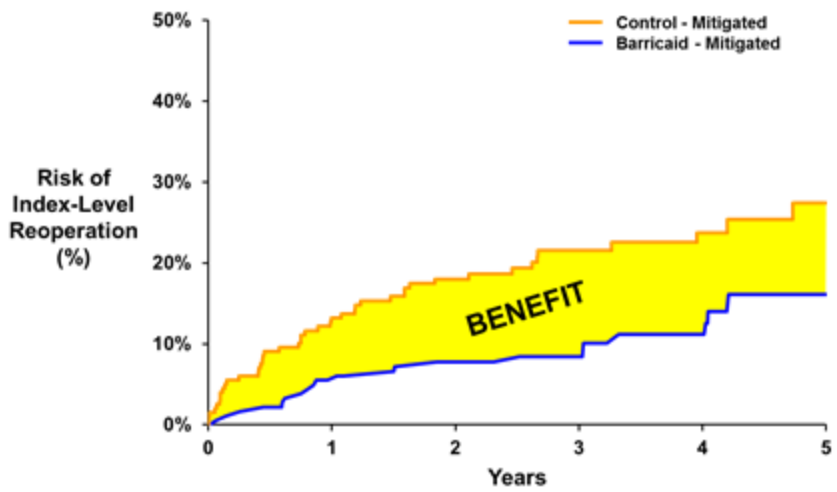
“Box” Anular Defect Geometry Did Not Alter Endpoint Outcome

Barricaid	Box	Other	Chi-squared p-value
Reherniation Success	49.4%	54.1%	0.505
CCS Composite Success	29.5%	24.1%	0.372
CCS-mCPD Modified Composite Success	77.5%	72.5%	0.391
No symptomatic reherniation	87.3%	91.9%	0.304
No secondary surgical intervention (SSI)	92.3%	89.4%	0.432

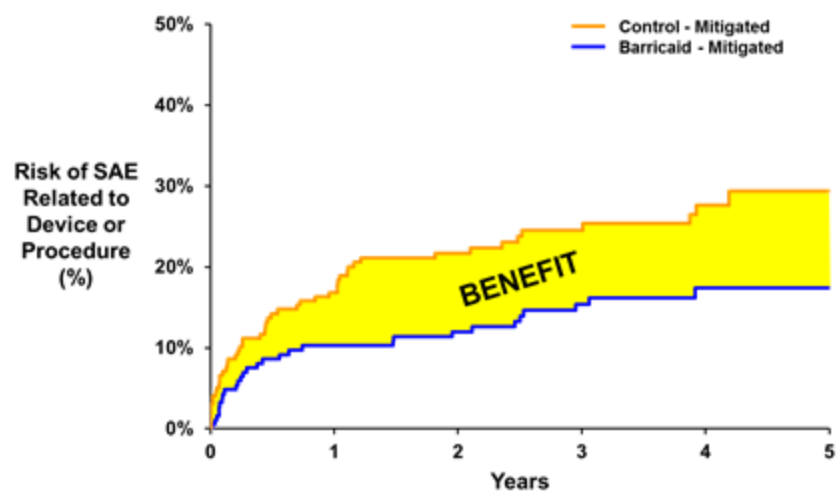
Control	Box	Other	Chi-squared p-value
Reherniation Success	29.5%	30.9%	0.801
CCS Composite Success	17.1%	19.5%	0.627
CCS-mCPD Modified Composite Success	66.7%	60.2%	0.287
No symptomatic reherniation	76.0%	72.7%	0.548
No secondary surgical intervention (SSI)	85.5%	81.5%	0.368

Significant Benefit Demonstrated

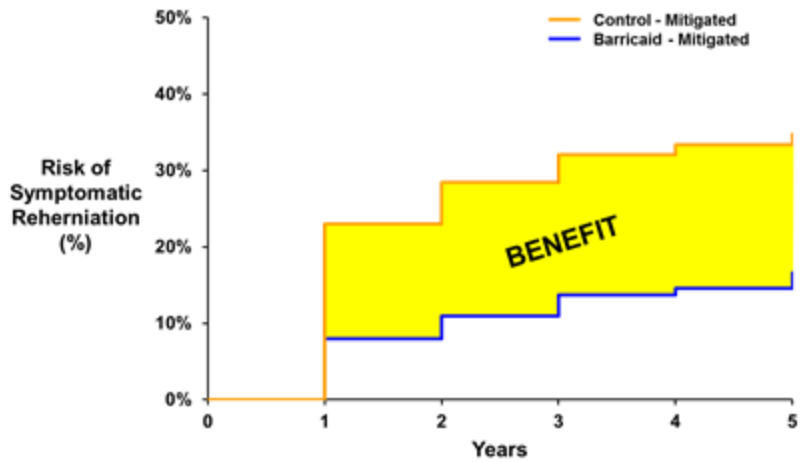
SSI



Related SAE



Symptomatic RH



Barricaid® Anular Closure Device

December 12, 2017

Intrinsic Therapeutics, Inc. (P160050)

Orthopaedic and Rehabilitation Devices Panel