

The SNAP Trial: 2-Year Results of a Double-Blind Multicenter Randomized Controlled Trial of a Silicon Nitride Versus a PEEK Cage in Patients After Lumbar Fusion Surgery

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Abstract

Study Design: Randomized controlled trial.

Objectives: Lumbar interbody fusion with cages is performed to provide vertebral stability, restore alignment, and maintain disc and foraminal height. Polyetheretherketone (PEEK) is commonly used. Silicon nitride (Si_3N_4) is an alternative material with good osteointegrative properties. This study was designed to assess if Si_3N_4 cages perform similar to PEEK.

Methods: A non-inferiority double-blind multicenter RCT was designed. Patients presenting with chronic low-back pain with or without leg pain were included. Single- or double-level instrumented transforaminal lumbar interbody fusion (TLIF) using an oblique PEEK or Si_3N_4 cage was performed. The primary outcome was the Roland-Morris Disability Questionnaire (RMDQ). The non-inferiority margin for the RMDQ was 2.6 points on a scale of 24. Secondary outcomes included the Oswestry Disability Questionnaire (ODI), Visual Analogue Scales (VAS), SF-36 Physical Function, patient and surgeon Likert scores, radiographic evaluations for subsidence, segmental motion, and fusion. Follow-up was planned at 3, 6, 12, and 24-months.

Results: Ninety-two patients were randomized (i.e. 48 to PEEK and 44 to Si_3N_4). Both groups showed good clinical improvements on the RMDQ scores of up to 5-8 points during follow-up. No statistically significant differences were observed in clinical and radiographic outcomes. Mean operative time and blood loss were statistically significantly higher for the Si_3N_4 cohort. Although not statistically significant, there was a higher incidence of complications and revisions associated with the Si_3N_4 cage.

Conclusions: There was insufficient evidence to conclude that Si_3N_4 was non-inferior to PEEK.

Keywords

polyetheretherketone (PEEK), silicon nitride (Si_3N_4), lumbar spinal fusion, degenerative disc disease, randomized controlled trial

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Introduction

Intervertebral fusion is one of the methods to treat chronic low back pain. Mechanical and biological factors play an important role in creating an optimal environment for bony fusion. Originally, stand-alone bone grafts were used, but they are associated with nonunion, collapse and donor side morbidity. Therefore they were succeeded by the use of interbody cages.¹ Interbody cages can be used to restore alignment and maintain disc- and foraminal height while facilitating bony fusion. PEEK has become one of the most frequently used materials with high fusion rates and good clinical results.² However, there are also disadvantages. PEEK's hydrophobic surface discourages direct appositional bone growth, which may lead to the formation of a fibrous layer around the implant.³ Ti surfaces can be more osteoinductive than PEEK, but they produce artifacts on CT and MRI and are associated with an increased risk of subsidence compared to PEEK.⁴ Latest developments focus on combining the 2 materials to optimize intervertebral fusion. For example, the enhancement of PEEK cages with Ti-coated endplates⁵ and hydroxyapatite coated PEEK cages can improve osteointegration.⁶ Still, no differences in clinical outcomes and fusion rates are reported between these materials.⁷

New materials like ceramics have been introduced. Silicon nitride (Si_3N_4) is such a (non-oxide) ceramic with high strength and toughness. Si_3N_4 minimizes scatter and artifacts on CT and MRI imaging.⁸ Due to its surface chemistry it allows a decreased bacterial activity compared to PEEK and Ti.⁹ Si_3N_4 received the CE Mark and FDA market clearance for its use as an interbody cage in 2008. It's mechanical, chemical and osteoconductive qualities were extensively described in literature.¹⁰ A recent animal study showed similar results in mechanical stability and bone formation of Si_3N_4 cages compared to the PEEK.¹¹ A RCT comparing PEEK and Si_3N_4 cages after anterior cervical discectomy with fusion (ACDF) reported no statistically significant differences in clinical outcome and fusion rates.¹² At the time of our study design, no clinical trial data of Si_3N_4 in the lumbar spine were published yet. Therefore, the Silicon Nitride And PEEK (SNAP) trial was designed to compare a PEEK cage with a Si_3N_4 cage in patients after lumbar fusion surgery.¹³ Primary objective was to show that lumbar spinal fusion with a Si_3N_4 cage produces similar improvement in clinical outcome compared to a PEEK cage. This article reports the 2-year outcomes.

Materials and Methods

Study Design

One hundred patients presenting with chronic low back pain with or without leg pain were treated with either a PEEK or Si_3N_4 cage. The study protocol was published in detail previously.¹³ In short, the study was designed as a non-inferiority multicenter clinical observer and patient blinded RCT. Inclusion criteria are listed in Table 1. Patients were randomly allocated by use of a centralized 24-hour online computerized randomization system (Sealed Envelope Ltd. London).

Table 1. Inclusion and Exclusion Criteria.

Inclusion criteria	<ul style="list-style-type: none"> – Male and female patients age 18-75 years – Chronic low back pain unresponsive to at least 6 months of conservative care – MRI and standing x-ray evidence of Pfirrmann Grade III or greater disc degeneration – Degeneration and/or degenerative or isthmic spondylolisthesis of Grade I or II – Signed informed consent
Exclusion criteria	<ul style="list-style-type: none"> – Osteoporosis – Patients with prior failed fusion at the same level – Degenerative scoliosis – Degenerative spondylolisthesis greater than Grade II – Pregnancy – Psychiatric or mental disease – Alcoholism (drinking more than 5 units per day) – Active infection or prior infection at the surgical site – Active cancer – Insufficient language skills to complete questionnaires – Participation in another study – More than 2 symptomatic levels that need fusion – Planned emigration abroad in the year after inclusion

Measurements were performed pre-operative and at 3, 6, 12 and 24 months.

Ethical Considerations

This study was performed in line with the principles of the Declaration of Helsinki. The protocol has been reviewed and approved by the local medical ethics committee (Verenigde Commissies Mensgebonden Onderzoek, as of Jan 1th 2015 known as Medical Research Ethics Committee United, Nieuwegein, the Netherlands. Approval number NL34808.100.10). Written informed consent was obtained from all individual participants included in the study. Authors were not exempt from requirement.

Surgical Procedure

Single- or double-level transforaminal lumbar interbody fusion (TLIF) with pedicle screw fixation was performed with either an oblique PEEK or Si_3N_4 cage (PhantomTMPLIF and Valeo[®]OL, respectively, CTL Medical, Dallas, TX, USA) (Figure 1A ~ B). The Si_3N_4 cage had a lordosis of 0° whereas the PEEK implant had 6° of lordosis. After adequate exposure and placement of pedicle screws, a facetectomy was performed followed by an appropriate decompression on the symptomatic site. The disc space was cleared from disc material and endplates were prepared. Cages were packed with autograft derived from locally harvested bone. A single oblique cage was placed in the prepared disc space. Final fixation of screws and

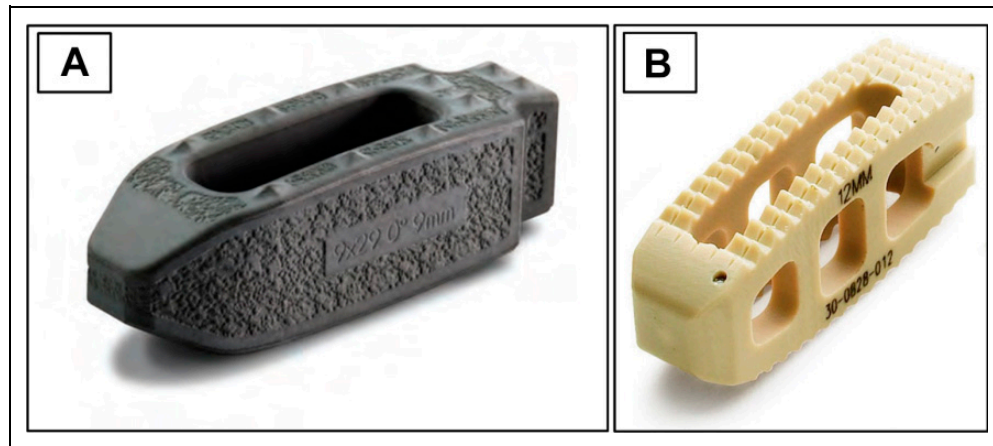


Figure 1. Lumbar intervertebral cages used in this study: (A) Valeo™ OL Si₃N₄ cage and (B) Phantom™ PLIF PEEK cage.

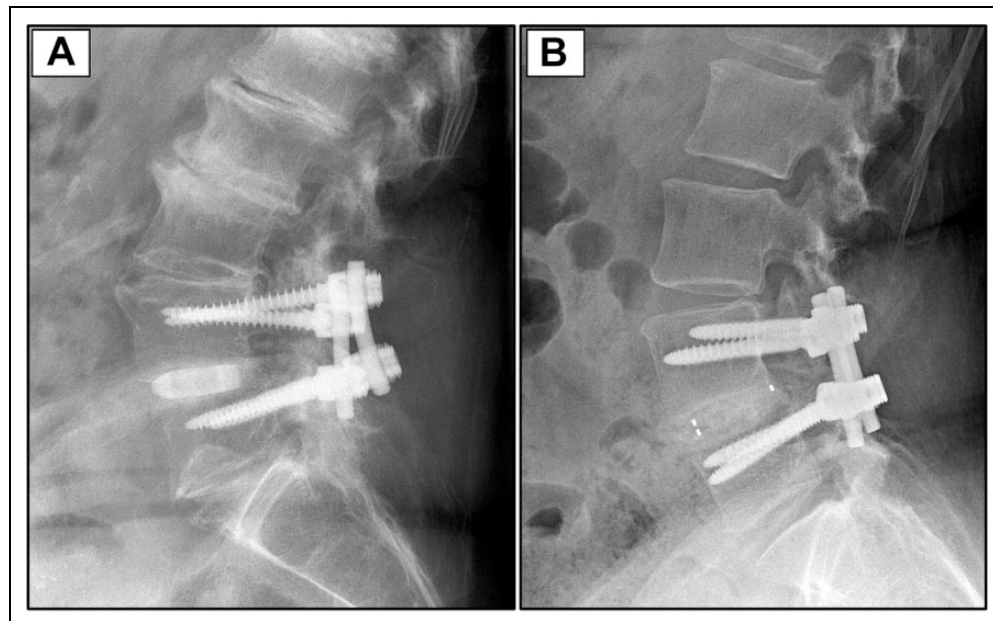


Figure 2. Lateral X-rays of L4-L5 fusion at 24-months for: (A) Si₃N₄ cage and (B) PEEK cage. Note that fusion was achieved with both cages as indicated by bone bridging between the endplates.

rods was performed under compression. Patients were mobilized on the first day after surgery without bracing.

Outcome Measures

Clinical assessment. The primary outcome measure was the Roland Morris Disability Questionnaire (RMDQ) (0-24 scale).¹⁴ Secondary outcome measures included scores from the generic quality of life questionnaire SF-36,¹⁵ Oswestry Disability Index (ODI, 0-50 scale),¹⁶ Visual Analog Scales for leg and back pain (VAS, 0 to 100 mm)¹⁷ and the 7-point Likert score for patient and surgeon perceived recovery in which “complete recovery” and “almost complete recovery” were considered good outcomes.¹⁸ In addition, a neurological examination was conducted at each follow-up.

Radiological assessment. Fusion status was evaluated according to the criteria described by Burkus et al.¹⁹ which included: (i) the presence of bridging bone on a computed tomography (CT) scan (Siemens Sensation 16, Malvern, PA, USA, 3.0 mm slice) at 12-months follow-up; (ii) disc height and angular changes in segmental alignment on lateral conventional radiographs (CR) during follow-up; and (iii) an assessment of device-host interface on a CT scan at 12-months follow-up.¹⁹ Standing anterior-posterior (AP) and lateral CR's were collected at 3, 6, 12, and 24-months of follow-up (Figure 2). Average disc heights were determined as the mean of the anterior and posterior measurements. Subsidence was defined as a loss of >1 mm in average disc height. At 24-months, additional flexion/extension standing lateral radiographs were obtained to monitor angular motion. Fusion was defined as an angular motion of <2° and

translational motion of < 0.5 mm. Each level was analyzed separately in cases with 2-level fusion. All radiological analyses were performed by radiologists from an independent organization (Medical Metrics, Houston, TX, USA).

Statistical Analyses

Primary efficacy analysis. The primary outcome was the RMDQ score. Primary objective was to demonstrate that the Si₃N₄ cage was non-inferior to the PEEK cage based on the primary comparison at 12 months. The considered non-inferiority margin was 2.6 points for the difference in RMDQ between the treatment arms.^{13,20} The analysis was based on a mixed-effects model for repeated measurements (MMRM). No imputation of missing data was performed. The MMRM model included treatment (type of cage) and center as factors, baseline RMDQ as covariate (fixed effects), and patient as random effect. An unstructured covariance matrix was assumed to model the within-patient variance and estimation was performed by restricted maximum likelihood method. Based on the model, the result of the contrast at 12 months is expressed with point estimate for difference in mean RMDQ between the 2 cages (Si₃N₄-PEEK) and one-sided confidence interval with significance level of 2.5%. Non-inferiority was to be demonstrated if the upper boundary of this confidence interval does not exceed the non-inferiority margin of 2.6 points. Assuming a standard deviation of 4 points, 50 patients per arm provide 90% power to demonstrate non-inferiority.¹³

Sensitivity analysis. To assess impact of drop outs, sensitivity analysis was performed. This analysis was conducted following Last Observation Carried Forward (LOCF) imputation. The analytical and estimation method for the sensitivity analysis was based on the same mixed-effects model for repeated measurements with the same terms as employed for the primary efficacy analysis (MMRM on the completed dataset).

Secondary efficacy analyses. The secondary efficacy outcomes assessed at each visit (ODI, Vas leg, VAS back, SF36 and radiological measurements) were analyzed using the same mixed-effects model for repeated measurements with the same terms as employed for the primary efficacy analysis. Dichotomous outcomes (dichotomized Likert scales for patient and surgeon perception) were compared between treatment groups based on Z-tests for comparing proportions. Statistical analyses were performed using RStudio and nlme. Plots were created using R base plotting functions and ggplot2.

Results

Baseline Characteristics

Between 2012 and 2015, 100 patients were included in 2 centers (49 and 51). Eight patients were subsequently excluded due to protocol violations (no randomization pre-operative, proof of osteoporosis after inclusion, age during surgery) or cancellation of surgery by the patient after inclusion. Of the remaining

Table 2. Baseline Characteristics.

	PEEK	Si ₃ N ₄
n	48	44
Age (mean (sd))	53.3 (9.2)	55.4 (11.5)
Gender = Female (%)	33 (68.8)	28 (63.6)
BMI (mean(sd))	27.1 (4.3)	27.1 (5.1)
Smoking = Yes (%)	31 (64.6)	32 (72.7)
Duration of complaints (mean (sd))	10.6 (9.3)	8.9 (6.1)
Type of complaints, n (%)		
Radicular pain	8 (16.7)	9 (20.5)
Combination back/radiculair	39 (81.2)	30 (68.2)
Back pain	1 (2.1)	5 (11.4)
Clinical diagnosis, n (%)		
Degenerative disc disease	10 (20.8)	13 (29.5)
Isthmic spondylolisthesis grade 1	12 (25.0)	11 (25.0)
Isthmic spondylolisthesis grade 2	5 (10.4)	6 (13.6)
Degenerative spondylolisthesis grade 1	20 (41.7)	14 (31.8)
Degenerative spondylolisthesis grade 2	1 (2.1)	0 (0.0)
Operated levels, n (%)		
1-level: L3-L4	4 (8.5)	5 (11.4)
L4-L5	15 (31.9)	11 (25.0)
L5-S1	21 (44.7)	19 (43.2)
L5-L6	1 (2.1)	0 (0.0)
L6-S1	1 (2.1)	1 (2.3)
2-level: L3-L5	2 (4.3)	1 (2.3)
L4-L6	0 (0.0)	1 (2.3)
L4-S1	3 (6.3)	5 (11.4)
L5-L6-S1	0 (0.0)	1 (2.3)
RMDQ (mean (sd))	14.2 (4.3)	14.8 (4.3)
ODI (mean (sd))	23.1 (7.4)	22.5 (7.0)
VAS leg (mean (sd))	60.9 (20.7)	58.9 (27.8)
VAS back (mean (sd))	62.3 (22.3)	61.7 (21.9)
SF-36 Physical Functioning (mean (sd))	37.0 (19.5)	39.9 (19.4)

92 patients (46 per each center), 48 were randomized for PEEK and 44 for Si₃N₄. Eight patients in the Si₃N₄ group received a 2-level fusion compared to 5 patients in the PEEK group. Baseline characteristics are shown in Table 2. At 24 months, 7 patients were lost to follow-up (7.6% drop-out rate).

Perioperative Results

Peri-operative data are shown in Table 3. There were no differences in length of hospital stay between both groups. Average operative time (Si₃N₄ 72-290 min vs PEEK 75-240 min) and blood loss (Si₃N₄ 120-1700 ml vs PEEK 100-700 ml) was significantly higher in the Si₃N₄ group. There was also a slightly higher peri-operative complication rate in the Si₃N₄ group, although these differences were not statistically significant (Table 3).

Clinical Outcome

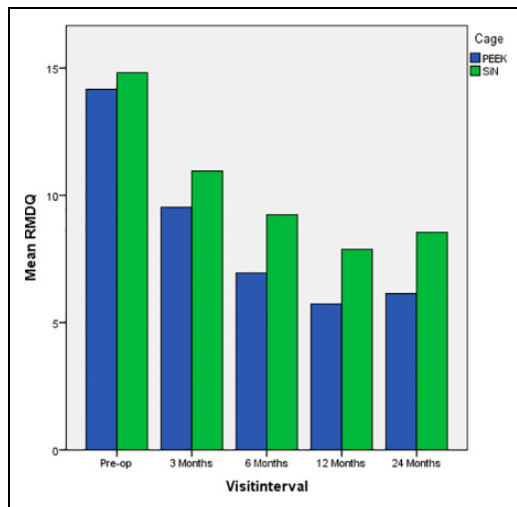
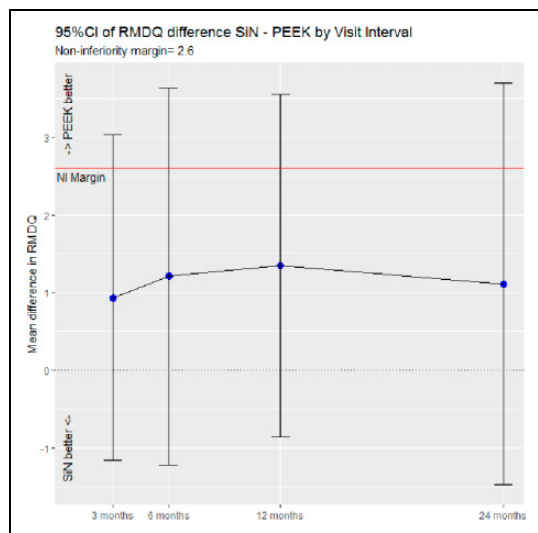
Both treatment arms showed good improvements in RMDQ scores during the 24-months follow-up (Figure 3). Although patients treated with PEEK had better outcomes at 3, 6, 12 and 24 months compared to Si₃N₄, these differences were not significant.

Table 3. Peri-Operative Characteristics.

	PEEK (n = 48)	Si ₃ N ₄ (n = 44)	P value
Operative time min (mean (sd))	127 (46)	150 (51)	0.03*
Blood loss ml (mean (sd))	317 (150)	473 (332)	0.01*
Hospital stay days (mean (sd))	3.8 (2.2)	3.8 (1.6)	0.90*
Complications, n (%):			
Dural tear	1 (2.1)	4 (9.1)	0.14**
Implant malposition	0 (0.0)	3 (6.8)	0.07**
Sensory deficit	1 (2.1)	3 (6.8)	0.27**
Motor deficit (MRC grade 4/5)	2 (4.2)	2 (4.2)	0.93**

*Two-sample t-test, p-value for difference 2-sided.

**Two-sample Z-test for equality of proportions, p-value for difference 2-sided.

**Figure 3.** RMDQ scores during follow-up.**Figure 4.** 95% CI of RMDQ difference between PEEK and Si₃N₄ by visit interval.**Table 4.** Outcome During Follow-Up.

	PEEK	Si ₃ N ₄	p value
Roland Morris Disability Questionnaire (sd) 0-24 scale			
3 months	9.5 (5.5)	11.0 (5.2)	0.19*
6 months	7.0 (6.3)	9.2 (6.7)	0.16*
12 months	5.7 (5.8)	7.9 (6.4)	0.11*
24 months	6.1 (6.5)	8.5 (7.0)	0.20*
Oswestry Disability Questionnaire (sd) 0-50 scale			
3 months	14.8 (9.4)	15.7 (8.0)	0.47*
6 months	10.7 (10.3)	12.3 (8.7)	0.49*
12 months	10.2 (10.2)	9.7 (9.1)	0.17*
24 months	11.9 (10.3)	11.2 (10.9)	0.40*
VAS leg (sd) 0-100 scale			
3 months	26.5 (27.7)	26.4 (26.2)	0.49*
6 months	23.6 (29.2)	26.2 (28.8)	0.47*
12 months	24.6 (28.4)	26.5 (22.9)	0.28*
24 months	26.3 (25.3)	30.0 (31.3)	0.31*
VAS back (sd) 0-100 scale			
3 months	34.9 (18.1)	37.9 (22.3)	0.49*
6 months	28.9 (23.3)	26.4 (25.4)	0.27*
12 months	30.2 (21.9)	31.0 (22.9)	0.39*
24 months	34.8 (24.7)	38.2 (25.7)	0.45*
SF36 physical functioning (sd)			
3 months	59.2 (20.6)	58.0 (17.2)	0.44*
6 months	66.0 (23.9)	61.2 (19.7)	0.25*
12 months	73.1 (23.1)	68.5 (21.2)	0.24*
24 months	71.5 (24.6)	64.9 (23.0)	0.20*
Surgeon perceived Likert (%)			
3 months	73.3	58.1	0.20**
6 months	76.2	61.0	0.20**
12 months	78.6	61.9	0.15**
24 months	78.0	56.3	0.08**
Patient perceived Likert (%)			
3 months	64.3	58.1	0.72**
6 months	76.2	56.1	0.09**
12 months	78.6	64.3	0.23**
24 months	75.0	50.0	0.05**
Disc height (mm)			
postoperative	8.3	8.1	0.63*
3 months	7.3	7.3	0.91*
6 months	7.2	7.0	0.67*
12 months	7.1	6.9	0.67*
24 months	7.1	6.9	0.68*
Translational motion (mm)			
24 months	0.12	0.14	0.70**
Angular motion (°) 24 months			
	0.94	1.18	0.24**

*Estimated from an MMRM model with the same specification as for the primary outcome analysis, p-value for difference one-sided.

**Two-sample t-test, p-value for difference 2-sided.

Using the a priori selected non-inferiority margin of 2.6, the null hypothesis that Si₃N₄ is non-inferior to PEEK could not be rejected. This is graphically shown in Figure 4. The upper boundary of the confidence interval exceeds the non-inferiority margin of 2.6 at each follow-up period.

Secondary outcomes are shown in Table 4. All patients showed good improvements during follow-up. There were no significant differences in VAS leg, VAS back, SF36 and ODI

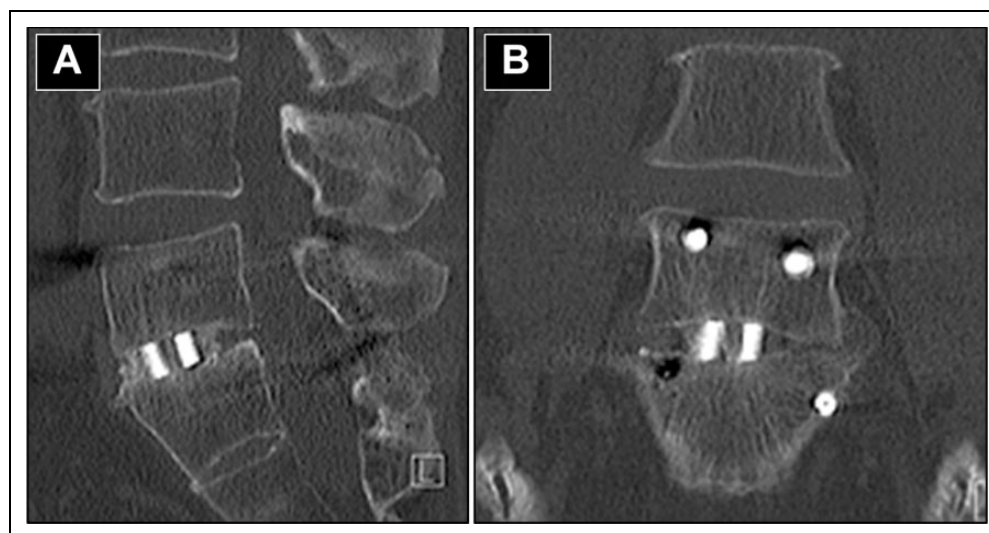


Figure 5. CT imaging of a Si_3N_4 cage at 12 months, showing bone bridging in the (A) sagittal and (B) coronal views. No signs of lucency were seen at the device-bone interface.

scores between the 2 groups. Although both surgeons and patients reported generally better recovery rates for the PEEK group at each follow-up time point, these differences did not reach statistical significance.

Radiological Outcomes

The radiographic data are also provided in Table 4. There were no significant differences in average disc heights between groups. Also, no significant differences in fusion rates were seen between the PEEK and Si_3N_4 based on the flexion/extension analysis of angular or translational motion (88% vs 82% respectively, $p = 0.40$). Bony bridging, measured on CT at 12 months, was seen in 42% vs 57% of patients in the PEEK and Si_3N_4 group respectively ($p = 0.13$). Sagittal and coronal views for a Si_3N_4 implant are shown in Figure 5 A ~ B. Due to the fact that PEEK cages are radiolucent, the interface between the endplates and these cages could not be adequately ascertained. An assessment of the device-bone interface (*i.e.*, radiolucency or osseous integration) was therefore deemed to be unreliable and could not be incorporated into the analyses.

Complications and Revisions

During 24 months follow-up there were 14 revisions (15.2% revision rate). Specifications are provided in Table 5. In the PEEK group 4 out of 48 patients (8.3%) were revised, compared to 10 out of 44 patients (22.7%) in the Si_3N_4 group ($p = 0.10$). Almost one-third of revisions were performed due to adjacent level problems (5 out of 14).

Discussion

The SNAP trial was designed to compare the clinical and radiological outcomes for Si_3N_4 cages versus PEEK cages

Table 5. Revision Surgery.

Cage	Index level	Time	Revision
PEEK	L4-S1	5 months	redecompression L5-S1
PEEK	L5-S1	7 months	redecompression L5-S1 + screw removal S1
PEEK	L4-L5	10 months	adjacent level L5-S1
PEEK	L3-L4	14 months	adjacent level L4-S1
Silicon Nitride	L5-S1	1 day	revision cage due to implant malposition
Silicon Nitride	L5-S1	2 days	revision screw L6 due to neurological disorder
Silicon Nitride	L5-S1	6 months	revision screw due to lose endcap
Silicon Nitride	L5-S1	7 months	redecompression L5-S1
Silicon Nitride	L4-S1	8 months	adjacent level L3-L4
Silicon Nitride	L3-L4	10 months	adjacent level L4-S1
Silicon Nitride	L5-S1	18 months	revision cage due to non-union/loosening screws
Silicon Nitride	L5-S1	18 months	revision cage due to loosening cage
Silicon Nitride	L3-L4	19 months	adjacent level L4-L5
Silicon Nitride	L5-S1	20 months	revision cage due to non-union.

in patients undergoing lumbar fusion surgery. The overall results indicate that patients treated with either cage material had comparable outcomes with respect to disability, pain, and fusion. In particular, the RMDQ improvements observed in this trial were in line with the results from other spinal fusion studies,^{21,22} thereby reflecting good 2-year clinical outcomes for both groups. The secondary outcome scores were also consistent with reported literature using PEEK cages, ranging from 24 to 36 for VAS back pain, 26 to 42 for VAS leg pain² and 9 to 20 for ODI.²³ Lastly, the fusion results observed were also found to be similar to values reported in literature.²

Primary Outcome

In this study, it was hypothesized that Si_3N_4 would be non-inferior to PEEK as measured by a non-inferiority margin of 2.6 points on RMDQ scores at 12-months follow-up. Although both implant groups had improvement scores of up to 5-8 points, there was insufficient evidence to conclude that Si_3N_4 was non-inferior to PEEK. As with any non-inferiority study, this does depend directly on the non-inferiority margin of 2.6 points improvement on RMDQ that was pre-determined. Our considerations are part of the protocol,¹³ but other perspectives could have been taken. For example, Stratford et al²⁴ reported that the minimum detectable difference between pre- and post-treatments in patient with low back pain varied based on the patient's initial RMDQ score. They concluded that clinically important changes in the RMDQ were 2 (for an initial score of 0 to 8), 4 (for an initial score of 5 to 12), 5 (for an initial score of 9 to 16), 8 (for an initial score of 13 to 20), and 8 (for an initial score of 17 to 24). Since in our study the initial RMDQ score was 14, a higher non-inferiority margin might have been chosen, although such a margin does not only depend on the minimal detectable difference at individual patient level. It does stress the importance of stratification of the patient population in assessing relevant pain scores, and should be taken into consideration for future studies.

Perioperative Outcomes

A significant difference was found in operative time and blood loss in favor of the PEEK cohort (*i.e.* 127 min vs 150 min and 317 ml vs 473 ml respectively). The greater amount of blood loss was directly linked to a longer operative time for the Si_3N_4 cohort. However, this result is skewed due to an outlier value of one patient in the Si_3N_4 group whose blood loss was 1700 ml. The difference in operative time can also be partially explained by a higher number of 2-level procedures in the Si_3N_4 cohort compared to PEEK (*i.e.*, 8 versus 5). Additionally, upon rotating the Si_3N_4 cage during insertion, in 2 patients a fracture occurred at the insertor-cage interface. These cages needed to be replaced, extending the operative time. After thorough analysis, the cause of these 2 incidents was found to be a lack of stability in the insertor-cage interface. After adjusting the tip of the insertor, which created a more stable grip while inserting the cage, no additional fractures occurred. Other perioperative complications were evenly distributed over the length of the study.

Radiological Outcomes

There is considerable controversy in the scientific literature as to when a lumbar segment is radiologically fused.^{19,25} Various criteria of angular and translational motions have been proposed, coupled with the presence of anterior bridging bone (*i.e.*, the "sentinel sign") without radiolucencies at the superior or inferior surfaces of the implant. In this study, as the PEEK cages were radiolucent, an assessment of either radiolucencies

around these cages and their osseous integration was deemed unreliable and therefore unusable for this analyses. However, several other criteria were usable. First, bony bridging was measured on CT at 12 months and defined as the presence of a bony bridge from one endplate to the next. Secondly, disc height measurements were used for analyses of potential subsidence. In both groups no statistically significant differences were seen in average amount of subsidence or bony bridging. Thirdly, segmental motion measured on flexion/extension radiograms was used to analyze fusion, defining angular motion $< 2^\circ$ and translational motion < 0.5 mm as fusion. This study showed fusion rates consistent with results found in literature.² However, a technically and/or radiographically insufficient fusion does not necessarily equate an unsuccessful clinical outcome because vertebral stability may occur before it is radiographically evident.²⁶ This could explain there is no clear evidence that a bony fusion correlates with a good clinical outcome.

Complications

There were more revisions within the Si_3N_4 group compared to the PEEK group (10 vs 4), however this difference was not statistically significant ($p = 0.10$) (Table 5). Most revisions were performed due to adjacent level problems. Also, as described earlier, two Si_3N_4 cages fractured during surgery at the insertor-cage interface due to a technical problem with the insertor.

Limitations

The design of the SNAP trial had several limitations. Firstly, the use of a single oblique cage was chosen to allow for more accurate fusion measurements on CT. However, a single cage is mechanically less stable compared to 2 parallel placed cages.²⁷ This could have biased the results and can also explain the high revision rate of 15.2%. Secondly, as discussed earlier we can reiterate the way our non-inferiority margin of 2.6 points improvement on RMDQ was determined. Thirdly, this study was funded by Amedica Corporation (Salt Lake City, UT, USA), the manufacturer of the Si_3N_4 cage. Every effort was made to eliminate bias in the study design, protocol, and management of the study. Independent Clinical Research Organization (CRO) managed the study together with the principal investigator's institution, the statistical analyses were performed by an independent organization employing their own statisticians (Julius Centre for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands) and yet another independent unit performed the radiographic measurements (Medical Metrix). With those precautions, the authors have implemented the most reasonable procedure to minimize bias.

Conclusions

Despite the fact that both groups in our trial had good clinical improvements on the RMDQ scores during follow-up of up to

5-8 points after 24 months, there is insufficient evidence to conclude that the Si₃N₄ cage is non-inferior to the PEEK cage. Perioperative blood loss and surgery time were significantly higher in the Si₃N₄ group. Additionally, a higher incidence of complications and a higher incidence of revisions seemed to be associated with the Si₃N₄ cage, although not statistically significant.

Authors' Note

The research departments of both participating centers were compensated for their time. The device(s)/drug(s) is/are FDA-approved or approved by corresponding national agency for this indication. Trial registration number: clinicaltrials.gov, Identifier: NCT01557829.

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Declaration of Conflicting Interests

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