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Clinical Study

A prospective, international, randomized, noninferiority study comparing an implantable titanium vertebral augmentation device versus balloon kyphoplasty in the reduction of vertebral compression fractures (SAKOS study)

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Abstract

BACKGROUND CONTEXT: Balloon kyphoplasty (BKP) is a commonly performed vertebral augmentation procedure for painful osteoporotic vertebral compression fractures (OVCFs).
OBJECTIVE: This study aimed to support a non-inferiority finding for the use of a titanium implantable vertebral augmentation device (TIVAD) compared to BKP.
STUDY DESIGN: Prospective, parallel group, controlled comparative randomized study.

FDA device/drug status: The devices are FDA approved or approved by corresponding national agencies for this indication. The SpineJack® is commercially available in Europe. KyphX Xpander® Inflatable Bone Tamp is commercially available in the United States and Europe.

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PATIENT SAMPLE: Patients who presented with one or two painful OVCFs located between T7 and L4 aged <3 months, failed conservative treatment, and had an Oswestry Disability Index (ODI) score ≥30/100 were eligible for the study.

OUTCOME MEASURES: The primary composite endpoint was defined as: reduction in VCF fracture-related pain at 12 months from baseline and maintenance or functional improvement (ODI) at 12 months from baseline, and absence of device-related adverse event or surgical reintervention. If the primary composite endpoint was successful, a fourth component (absence of adjacent level fracture) was added for analysis. If the analysis of this additional composite endpoint was successful, then midline target height restoration at 6 and 12 months was assessed. Secondary clinical outcomes included back pain intensity, ODI score, EQ-5D index score (range 0=death to 1=full health) and EQ-VAS score (range 0−100).

METHODS: Patients were recruited in 13 hospitals across 5 countries and were randomly assigned (1:1) to either TIVAD or BKP with electronic randomization as described in the protocol. A total of 152 patients with OVCFs were initially randomized. Eleven patients were excluded (six met exclusion criteria, one with evidence of tumor, and four patients had T score out of requested range). Anterior vertebral body height ratio, midline vertebral body height ratio, and Cobb angle were measured preoperatively and postoperatively by an independent imaging core lab. Adjacent and subsequent fractures and safety parameters were recorded throughout the study. Cement extravasation was evaluated on X-rays. All patients were followed at screening at 5 days, 1 month, 6 months, and 12 months postoperatively. This study was supported by Vexim SA. Seven authors received study-specific support less than $10,000 per year and seven authors received no study-specific support.

RESULTS: Among the 141 patients (78.7% female, mean age 73.3±9.5 years) who underwent surgery (TIVAD=68; BKP=73), 126 patients (89.4%) completed the 12-month follow-up period (TIVAD=61; BKP=65). The analysis of primary endpoint on the ITT population demonstrated non-inferiority of the TIVAD to BKP. The analysis of the additional composite endpoint demonstrated the superiority of TIVAD over BKP ($p<0.0001$) at 6 months (88.1% vs. 60.9%) and at 12 months (79.7% vs. 59.3%). Midline VB height restoration was more improved for TIVAD than for BKP at 6 months (1.14±2.61 mm vs. 0.31±2.22 mm); $p=0.0246$) and 12 months after surgery (1.31±2.58 mm vs. 0.10±2.34 mm; $p=0.0035$). No statistically significant differences were shown between procedures for improvement in functional capacity and quality of life. Pain relief was significantly more marked in the TIVAD group compared to the BKP group at 1 month ($p=0.029$) and at 6 months ($p=0.021$) after surgery. No patient required surgical reintervention or retreatment at the treated level. No symptomatic cement leakage was reported. Adverse events were similar for both groups (41.2% in the TIVAD group and 45.2% in the BKP group). The incidence of adjacent fractures was significantly lower after the TIVAD procedure than after BKP (12.9% vs. 27.3%; $p=0.043$).

CONCLUSIONS: Study results demonstrated non-inferiority of the TIVAD to the predicate BKP with an excellent risk/benefit profile for results up to 12 months.

Keywords: Adjacent fractures; Balloon kyphoplasty; Height restoration; Osteoporosis; Percutaneous vertebral augmentation; Prospective randomized study; SpineJack® system; Spine surgery; Vertebral compression fracture

Introduction

Vertebral compression fractures (VCFs) are the most common osteoporotic fractures worldwide, occurring in 30% to 50% of people over the age of 50. VCFs affect an estimated 1.4 million patients in the world annually and incidence rates rise exponentially with age, especially in women [1,2]. In 2010, 5.2 million non-traumatic fractures were expected in the 12 industrialized countries studied, of which 2.8 million were at the hip or spine [3]. However, two-thirds to three-quarters of vertebral fractures are not recognized at the time of clinical occurrence [4]. Conservative treatment, which consists of pain medication, bed rest and braces, focuses on alleviating symptoms and supporting the spine. However, there are significant negative effects due to bed rest, opioids, and non-steroidal anti-inflammatory drugs, especially in the elderly. Open surgery (spine stabilization using screws and rods) is limited by easy pull-out of bone screws due to underlying bone disease [5]. Thus, VCFs frequently result in significant morbidity and health-care resource use [6]. Furthermore, clinically evident osteoporotic VCFs are associated with an increase in mortality risk [7].

In April 2013, the National Institute for Health and Care Excellence (NICE) recommended vertebral augmentation procedures (VAPs), namely percutaneous vertebroplasty and balloon kyphoplasty (BKP), as treatment options for patients with severe and disabling pain after a recent osteoporotic VCF. NICE further concluded it was reasonable to assume that vertebroplasty and kyphoplasty reduce mortality [7].

Vertebral augmentation can also be achieved by percutaneous implant techniques using expandable bone implant systems. These expandable implants are inserted before the injection of the bone cement in order to prevent the secondary loss of vertebral body (VB) height observed with BKP after balloon deflation [8].

A recent systematic review compared the efficacy and harms of BKP versus nonsurgical management, sham control, vertebroplasty, and an implant technique. The authors concluded that, based on a small number of heterogeneous (and high risk of bias) studies, there was no difference between BKP and other vertebral augmentation techniques, and that future randomized studies with adequately powered responder analyses for efficacy outcomes are needed [9].

A titanium implantable vertebral augmentation device (TIVAD) has been marketed in Europe since 2012 and recently obtained FDA 510(K) clearance in September 2018. This device has been shown in biomechanical studies to be superior to BKP in terms of sagittal height restoration and height maintenance [10,11]. Clinical data confirmed these advantages with a recent 1-year randomized clinical study that showed throughout the follow-up period a better middle VB height restoration with percentages of correction significantly higher compared to BKP [5]. These results were in line with preliminary results observed at 1 year by Vanni et al. [12].

BKP is the most commonly performed VAP, with 73% of VAPs performed in the United States between 2005 and 2010 [13]. In 2013, approximatively 147,060 VAPs were performed worldwide based on the Market Research of Millennium Inc. This prospective study aimed to compare the safety and effectiveness of the TIVAD with the KyphX Xpander Inflatable Bone Tamp (BKP) in the treatment of patients with painful osteoporotic VCFs and to support a non-inferiority finding for the use of the TIVAD versus BKP.

Methods

Study design and oversight

A prospective, international, multicenter, randomized, comparative study was conducted in 13 hospitals in Europe (5 in France, 3 in Germany, 1 in Italy, 2 in Spain, and 2 in Switzerland). Patients were considered eligible for inclusion if they met the following criteria: (1) male or female aged at least 50 years or older, (2) had radiographic evidence of 1 or 2 painful VCFs from T7 to L4 due to osteoporosis, (3) fracture (s) aged <3 months, and (4) fracture(s) that showed a loss of height in the anterior, middle, or posterior third of the VB ≥15% but ≤40%. A DEXA was performed to check if the patients presented osteoporosis with a T-score ≤−2.0. Patients were required to have undergone conservative therapy (bed rest, analgesic pain medication, and medications to address underlying osteoporosis such as bisphosphonates) for at least 6 weeks before enrollment. Patients who failed conservative medical therapy, defined as either having a VAS back pain score ≥50 mm at 6 weeks after initiation of fracture care or a VAS back pain score ≥70 mm at 2 weeks after initiation of fracture care, were considered eligible. Patients must also have had an Oswestry Disability Index (ODI) score ≥30%. The list of all selection criteria is available in Table 1.

Table 1
Main selection criteria

Inclusion criteria	Non-inclusion criteria
Male or female with at least 50 years of age.	Target VCF(s) due to underlying or suspected tumor, high-energy trauma, osteonecrosis.
Radiographic evidence of one or two painful VCF(s) between T7 and L4, aged <3 months, due to primary or secondary osteoporosis:	Segmental kyphosis of target vertebra of >30°.
o With a loss of height in the anterior, mid or posterior third of the VB from estimated prefracture configuration of at least 15% but not more than 40% based on X-Ray at baseline,	Previous surgical treatment at the VCF index level(s).
o With index fracture acute or persistent (not healed) as demonstrated by T2-weighted STIR MRI (or bone scan if patient is contraindicated for MRI).	Spinal canal compromise causing clinical manifestations of cord, neural foramen, or nerve root compression at the level(s) to be treated.
Patient who failed conservative medical therapy, defined as either having a VAS back pain score of ≥50 mm at 6 weeks after initiation of fracture care or a VAS back pain score of ≥70 mm at 2 weeks after initiation of fracture care.	Any physical exam evidence of myelopathy or radiculopathy, pre-existing or clinically unstable neurologic deficit.
NB. If patients with pain ≥70 mm at baseline continued to deteriorate as demonstrated by increasing VAS score and/or progressive vertebral collapse, treatment might be initiated after 1 week of conservative care.	Pain based on clinical diagnosis of herniated nucleus pulposus or severe spinal stenosis (progressive weakness or paralysis).
Investigator believed target VB was suitable for TIVAD and BKP (eg, appropriate pedicle diameter) assessed on CT scan pre-op, to assess the feasibility of the procedure in term of pedicle diameter.	Any radiographic evidence of pedicle fracture visible on pre-op CT scan, spondylolisthesis >Grade 1 at target VB(s).
Patient with ODI score ≥30/100.	Any underlying systemic bone disease other than osteoporosis.
Patient mentally capable and willing to sign a study specific informed consent prior to any study procedures.	Not able to walk without assistance before fracture(s).
Patient willing and able to comply with all study requirements including follow-up visits and radiographic assessments.	Pain due to any other condition that required daily narcotic medication, disabling back pain due to causes other than acute fracture(s).
	Medical contraindication to spinal surgery and/or general anesthesia, such as coagulopathy and/or regular intake of anticoagulants.
	Body mass index >40.

TIVAD, titanium implantable vertebral augmentation device; BKP, balloon kyphoplasty; ODI, Oswestry Disability Index; VAS, visual analogue scale; VCF, vertebral compression fracture.

The study protocol was approved by relevant ethics committees before implementation. All study procedures complied with the International Conference on Harmonization Good Clinical Practice (ICH GCP E6 R2), the Declaration of Helsinki, ISO 14155, and all applicable country-specific regulations. All eligible patients provided written informed consent before participating in any study-related activities. The study is registered with ClinicalTrials.gov, number NCT02461810.

Randomization and blinding

Once a subject satisfied all inclusion criteria to participate in the study, the investigator randomized the subject by connecting to an electronic randomization system provided by Medpass International (Paris, France) which indicated the treatment group assigned to the subject. An email was then sent to the investigator confirming the treatment allocated. Treatment assignment was 1:1 between the study procedure and the control procedure.

The investigators could not mask treating clinicians or patients to treatment allocation and patients were aware of their treatment group before receiving the procedure. Three independent experienced radiologists (two first-reviewers and one final decision maker) were completely blinded to (1) any personal data of the patient as well as any site-specific information, (2) study timepoints, (3) the results of the study (average descriptive radiographic results, patient reported outcomes, etc.) as well as to their own evaluations of the same patient at a certain different time point.

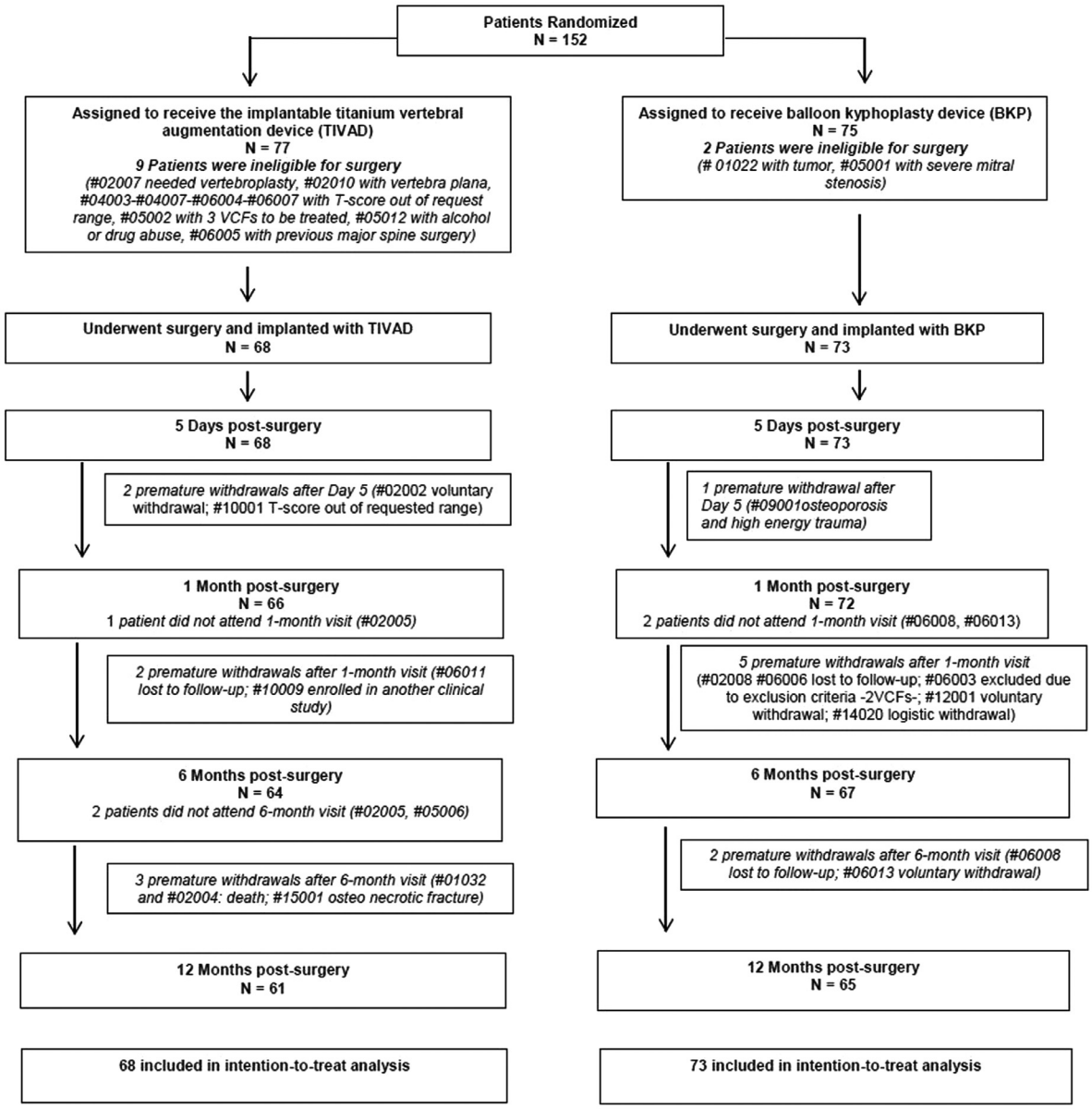
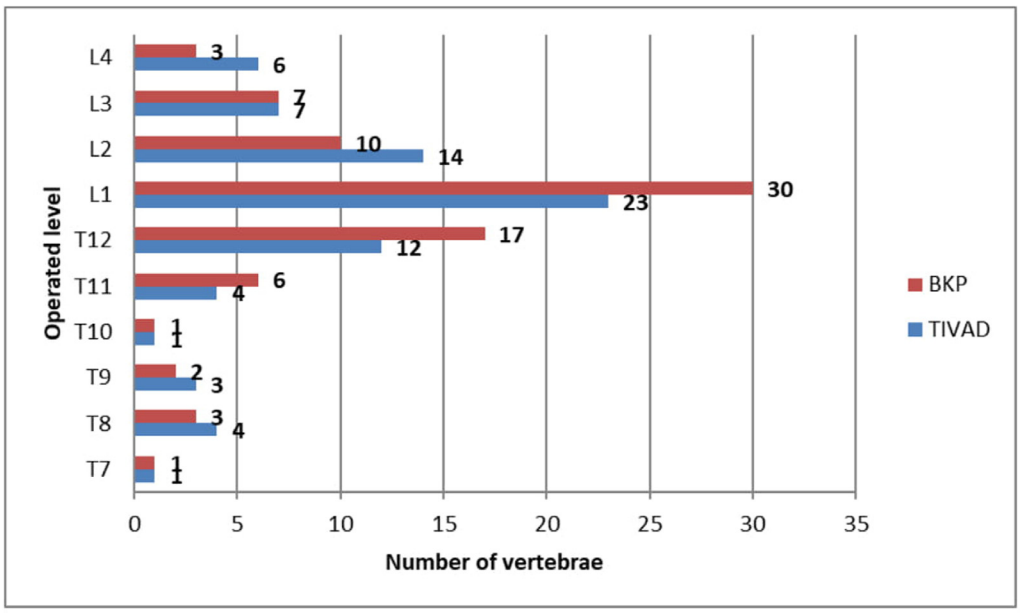


Fig. 1. Consort flow diagram.

Procedures

Both the TIVAD (SpineJack® system—Vexim SA) and KyphX Xpander® Inflatable Bone Tamp (Kyphon Inc., USA) are CE-marked devices that were used in accordance with their intended use.

Preoperative imaging was utilized to confirm that the study technique could safely be performed. After measuring the percent of loss of height on X-ray, fracture acuity was assessed using T2-weighted STIR MRI (or bone scan if patients were contraindicated for MRI). The feasibility of



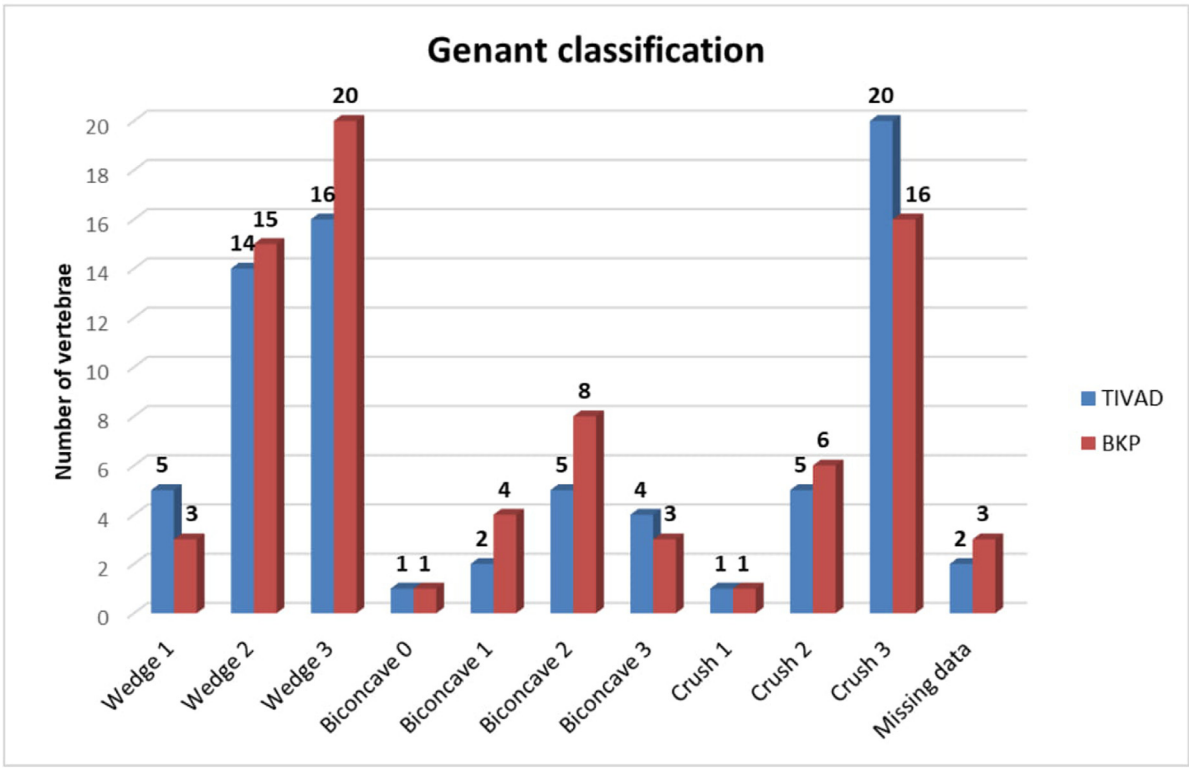


Fig. 2. Location, morphologic type, and severity of fractures according to the Genant's semiquantitative method. TIVAD, implantable titanium vertebral augmentation device; BKP, balloon kyphoplasty.

the procedure was evaluated by measurement of the pedicle diameter on CT scan.

All TIVAD procedures were conducted under general or local anesthesia. The VB was accessed through a standard transpedicular approach. The operative technique has been described in a previous study by Noriega et al. [14]. The control treatment arm used BKP with the KyphX® HV-R™ Bone Cement (Kyphon Inc, USA). The procedure was carried out according to the IFU via a bilateral approach using two balloons.

At each post-procedure clinic visit (5 days, 1 month, 6 months, and 12 months), adverse events (AEs), concomitant diseases, analgesic consumption, back pain intensity on 100-mm VAS [15], ODI score [16], and ambulatory status were recorded. A neurologic examination was performed during the day 5 clinic visit. Quality of life was evaluated at 1, 6, and 12 months using the EuroQol 5-domain (EQ-5D) questionnaire [17,18]. Lateral and AP spine X-rays were taken at each visit and read centrally according to a radiological protocol by a validated core laboratory (ACES Ing.-GmbH/Raylytic, Germany) for measurement of VB height (6-point morphometric measurements of the anterior, mid and posterior parts of the VB), and Cobb angle (defined as the angle formed by lines drawn parallel to the superior endplate of the VB above and the inferior endplate of the VB below). Radiographic reviews were performed independently by experienced radiologists blinded to treatment. CT was taken to evaluate integrity of the posterior elements and measure pedicle diameter and vertebral body length. The study flow chart is available on line.

Outcomes

The primary endpoint was the 12-month responder rate based on a composite endpoint of three components. This included a reduction of pain intensity at 12 months by >20 mm as measured by a 100-mm VAS, maintenance or improvement of the ODI score at 12 months, and absence of device-related AEs or symptomatic cement extravasation requiring surgical reintervention or retreatment at the index level. If the primary composite endpoint analysis was successful, a fourth component (which included absence of adjacent level fractures) would be added to the three components of the primary endpoint for further analysis. If the latter analysis was successful, then midline target height restoration at 6 and 12 months was to be tested for superiority versus BKP.

Secondary clinical outcomes included changes from baseline in back pain intensity, ODI score, EQ-5D index score (range 0=death to 1=full health) and EQ-VAS score (range 0–100), ambulatory status, analgesic consumption, and length of hospital stay. The percentage of patients with a reduction in pain by >20 mm and the percentage of patients with a maintenance or improvement in functional

Table 2
Demographics, preoperative characteristics, surgical procedure*

	TIVAD N=68	BKP N=73	Total N=141	p Value Between-group test
Sex, male/female no. (%)	17/51 (25.0/75.0)	13/60 (17.8/82.2)	30/111 (21.3/78.7)	0.297 (Chi-square)
Age (years)	74.4±8.9	72.2±10.0	73.3±9.5	0.287 (Wilcoxon)
Weight (kg)	64.7±12.2	65.9±12.0	65.4±12.1	0.565 (Student)
Height (m)	1.62±0.09	1.62±0.09	1.62±0.09	0.814 (Student)
BMI (kg/m^2)	24.6±3.9	25.2±4.1	24.9±4.0	0.376 (Student)
Back pain on VAS (mm)†	7.83±0.95	7.86±1.19	7.84±1.08	0.967 (Wilcoxon)
ODI score‡	65.0±15.5	66.0±16.0	65.5±15.7	0.606 (Wilcoxon)
EQ-VAS score§	47.5±21.6	45.8±18.3	46.6±19.9	0.622 (Student)
EQ-5D index score‖	0.29±0.25	0.25±0.22	0.27±0.23	0.357 (Wilcoxon)
Time since symptoms appearance (d)	36.6±20.5	36.4±21.9	36.5±21.2	0.854 (Wilcoxon)
Surgical procedure				
Anesthesia no. (%)				
General	45 (66.2)	51 (69.9)	96 (68.1)	0.240 (Fisher)
Local with conscious sedation	19 (27.9)	22 (30.1)	41 (29.1)	
Local without conscious sedation	3 (4.4)	0	3 (2.1)	
Spinal	1 (1.5%)	0	1 (0.7%)	
Procedure duration (min)	28.4±11.3	31.1±12.7	29.8±12.1	0.175 (Wilcoxon)
Total cement volume (mL)	4.1±1.7	5.9±2.3	5.0±2.2	**<0.001** (Wilcoxon)
Length of hospital stay (days)	3.8±3.6	3.3±2.4	3.5±3.1	0.926 (Wilcoxon)

TIVAD, titanium implantable vertebral augmentation device; BKP, balloon kyphoplasty; BMI, body mass index; EQ-5D, EuroQol 5-domain questionnaire. Bolded values indicate statistical significance to $p < 0.05$.

* Plus-minus values are mean±SD.

† Scores on the visual analog scale (VAS) range from 0 to 100, with higher scores indicating more severe pain.

‡ Scores on the Oswestry Disability Index (ODI) range from 0 to 100, with higher scores indicating more severe disability.

§ The EQ-VAS score ranges from 0 ("Worst imaginable health state") to 100 ("Best imaginable health state").

‖ The EQ-5D index score ranges from 0 (equal to death) to 1 (full health).

capacity were also assessed at each follow-up visit. Radiographic endpoints included restoration of vertebral body height (mm), and Cobb angle at each follow-up visit. AEs were recorded throughout the 12-month study period and classified according to MedDRA version 18.1 [19]. All device deficiencies and malfunctions were documented.

Statistical analysis

The study was powered based on an assumption of a 90% control responder rate, with 1% superiority in the TIVAD arm, and an estimated 15% loss to follow-up rate. A total sample size of 152 patients was selected to ensure at least 81% power.

The primary analysis was a test of non-inferiority of the success rate for the primary composite endpoint, using the ITT population (141 patients randomized and treated) and a non-inferiority margin of 15%. This primary analysis was a Bayesian test of the hypothesis H0: pc-ps≥0.15 versus H1: pc-ps<0.15 (pc and ps representing the success rates for the control and TIVAD arms), using multiple imputation to account for loss to follow-up. Confirmatory analyses of the primary endpoint were performed using observed performance based on available data (observed cases, no imputation), in the ITT and per protocol (PP) populations. Sensitivity analyses were also conducted to evaluate the impact of missing data by first treating all missing data as failures and then as successes.

The additional composite endpoint and midline target height restoration at 6 and 12 months were tested for superiority versus control on both ITT and PP populations, using a *t* test with one-sided 2.5% alpha. All secondary endpoints were compared between groups using appropriate bilateral statistical tests at the 5% significance level. All analyses were performed using SAS System version 9.4.

Results

From April 2015 through February 2017, 152 patients were randomized to either TIVAD group (n=77) or BKP group (n=75). After screening, a total of 11 patients (9 randomized to TIVAD and 2 randomized to BKP) were found to be ineligible for surgery and, therefore, did not undergo the procedure. Thus, 141 patients underwent surgery. Of these patients, 68 were implanted with the TIVAD (75 VCFs

Table 3
Efficacy results on primary composite endpoint and additional composite endpoint

	TIVAD N=68	BKP N=73	p Value (Non-inferiority test)
Primary composite endpoint			
Analysis in observed cases			
At month 6	N=59	N=63	
Responder rate	55/59 (93.2%)	53/63 (84.1%)	<0.0001
95% CI	86.8%–99.6%	75.1%–93.2%	
At month 12	N=59	N=55	
Responder rate	53/59 (89.8%)	48/55 (87.3%)	0.0016
95% CI	82.1%–97.5%	78.5%–96.1%	
Sensitivity analysis replacing missing data with failure			
At month 6	N=68	N=73	
Responder rate	55/68 (80.9%)	53/73 (72.6%)	0.0005
95% CI	71.5%–90.2%	62.4%–82.8%	
At month 12	N=68	N=73	
Responder rate	53/68 (77.9%)	48/73 (65.8%)	0.0001
95% CI	68.1%–87.8%	54.9%–76.6%	
Sensitivity analysis replacing missing data with success			
At month 6	N=68	N=73	
Responder rate	64/68 (94.1%)	63/73 (86.3%)	<0.0001
95% CI	88.5%–99.7%	78.4%–94.2%	
At month 12	N=68	N=73	
Responder rate	62/68 (91.2%)	66/73 (90.4%)	0.0006
95% CI	84.4%–97.9%	83.7%–97.2%	
Additional composite endpoint			
Analysis in observed cases			
At month 6	N=59	N=64	
Responder rate	52/59 (88.1%)	39/64 (60.9%)	<0.0001
95% CI	79.9%–96.4%	49.0%–72.9%	
At month 12	N=59	N=59	
Responder rate	47/59 (79.7%)	35/59 (59.3%)	<0.0001
95% CI	69.4%–89.9%	46.8%–71.9%	

TIVAD, titanium implantable vertebral augmentation device; BKP, balloon kyphoplasty.
Data are n/n (%); 95% CI.

treated as 7 patients had 2 fractures) and 73 underwent BKP (80 VCFs treated as 7 patients had 2 fractures). Following surgery, 15 patients (10.6%) withdrew prematurely or were lost to follow-up during the study (7 patients in the TIVAD group and 8 patients in the BKP group). In total, 126 patients completed the 12-month follow-up period. This included 61 patients in the TIVAD group and 65 patients in the BKP group (Fig. 1).

Location, morphologic type, and severity of the 155 treated fractures are presented in Fig. 2. No clinically relevant differences were observed between groups for demographics and main preoperative characteristics (Table 2). As shown in Table 2, the quantity of cement injected was significantly lower in the TIVAD group (p<0.001).

The Bayesian analysis of the primary endpoint concluded that TIVAD procedure was non-inferior to BKP 1 year after surgery as the posterior probability (0.09969) successfully met the criteria for study success (>0.987). Frequentist analysis on ITT population using the observed case method confirmed that TIVAD procedure was noninferior to BKP with 12-month responder rates of 89.8% and 87.3%, respectively (p=0.0016), and sensitivity analyses led to the same conclusion (Table 3). In the PP population, sensitivity analyses were performed to replace missing data with data that failed to meet the primary endpoint to confirm that missing data would not adversely affect the overall results. Even when replacing missing data with failure, TIVAD continued to demonstrate superiority TIVAD over BKP 12 months after surgery (82.8% responder rate vs. 67.1% responder rate, respectively; p<0.0001). At any time point, despite the methodology used, percentages of responders were in favor of TIVAD in both ITT and PP populations (Table 3).

The analysis of the additional composite endpoint demonstrated the superiority of TIVAD over BKP (p<0.0001) at 6 months (88.1% vs. 60.9%) and at 12 months (79.7% vs. 59.3%; Table 3). With regards to midline VB height restoration, when testing this parameter for superiority versus control using a *t* test with one-sided 2.5% alpha, the restoration achieved with TIVAD procedure in the ITT population was significantly greater than with BKP at 6 months (1.14±2.61 mm vs. 0.31±2.22 mm; p=0.0246) and at 12 months (1.31±2.58 mm vs. 0.10±2.34 mm; p=0.0035; Table 4). Similar results were observed in the PP population.

Bilateral statistical tests at the 5% significance level also showed that midline VB height restoration was significantly

Table 4
Midline vertebral body height restoration (changes expressed in mm)

	TIVAD N patients=68	BKP N patients=73	p Value
One-sided *t* test, 2.5% alpha (test for superiority)			
Restoration between baseline and month 6	N vertebrae=66	N vertebrae=68	
Mean±SD	1.14±2.61	0.31±2.22	
Median	0.90	0.50	**0.0246**
Range	−7.70 to 9.90	−9.70 to 5.30	
Restoration between baseline and month 12	N vertebrae=65	N vertebrae=61	
Mean±SD	1.31±2.58	0.10±2.34	
Median	1.00	0.30	**0.0035**
Range	−5.40 to 8.80	−9.80 to 5.40	
Two-sided Wilcoxon test, 5% alpha			
Restoration between baseline and day 5	N vertebrae=73	N vertebrae=74	
Mean±SD	2.69±2.40	1.28±1.81	
Median	2.40	0.75	**<0.001**
Range	−2.20 to 11.00	−4.40 to 5.70	
Restoration between baseline and month 1	N vertebrae=66	N vertebrae=67	
Mean±SD	1.95±2.32	0.52±2.15	
Median	1.35	0.30	**<0.001**
Range	−3.40 to 9.50	−8.70 to 5.30	
Restoration between baseline and month 6	N vertebrae=66	N vertebrae=68	
Mean±SD	1.14±2.61	0.31±2.22	
Median	0.90	0.50	0.121
Range	−7.70 to 9.90	−9.70 to 5.30	
Restoration between baseline and month 12	N vertebrae=65	N vertebrae=61	
Mean±SD	1.31±2.58	0.10±2.34	
Median	1.00	0.30	**0.041**
Range	−5.40 to 8.80	−9.80 to 5.40	

TIVAD, titanium implantable vertebral augmentation device; BKP, balloon kyphoplasty. Bolded values indicate statistical significance to p < 0.05.
Data were available at both baseline and day 5 for 147 out of 155 treated vertebrae.
Data were available at both baseline and month 1 for 133 out of 155 treated vertebrae.
Data were available at both baseline and month 6 for 134 out of 155 treated vertebrae.
Data were available at both baseline and month 12 for 126 out of 155 treated vertebrae.

greater with the TIVAD at 5 days and 1 month post-surgery (Table 4). No statistically significant between-group differences were found for the anterior and posterior portions of the VB. For Cobb angle evolution, no significant difference was shown between the procedures throughout the study.

Results on pain, functional capacity, and quality of life are displayed in Table 5 and Fig. 3. Five days after surgery, there was a marked reduction in pain in both groups. A progressive improvement was observed over the follow-up period in the TIVAD group only, and the decrease in pain intensity versus baseline was more pronounced in the TIVAD group compared to the BKP group at 1 month (p=0.029) and 6 months (p=0.021). At each time point, the percentage of patients with reduction in pain intensity >20 mm was ≥90% in the TIVAD group and ≥80% in the BKP group, with a statistically significant difference in favor of TIVAD at 1 month postprocedure (93.8% vs. 81.4%; p=0.030).

A sustained progressive improvement in disability was observed over the follow-up period in both groups. Although no statistically significant difference was found between groups during the follow-up period, there was a numerically greater improvement in the TIVAD group at most time points. At each time point, the percentage of patients with maintenance or improvement in functional capacity was at or close to 100%. In both groups, a clear and progressive improvement in quality of life was observed throughout the 1-year follow-up study period without any statistically significant between-group difference.

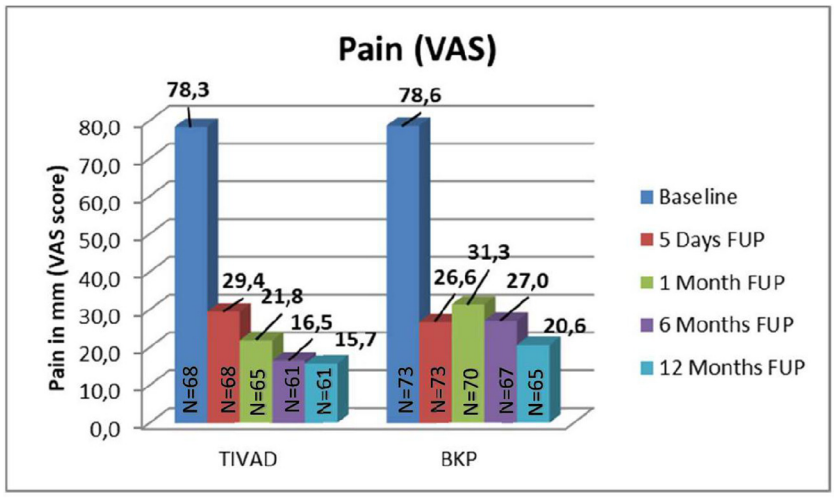
At 5 days post-surgery, neurological examination was normal in all patients. At each time point, in both groups, more than 80% of patients were able to walk without assistance. Five days after surgery, there were significantly less patients taking central agents in the TIVAD group compared to the BKP group (7.4% vs. 21.9%; p=0.015).

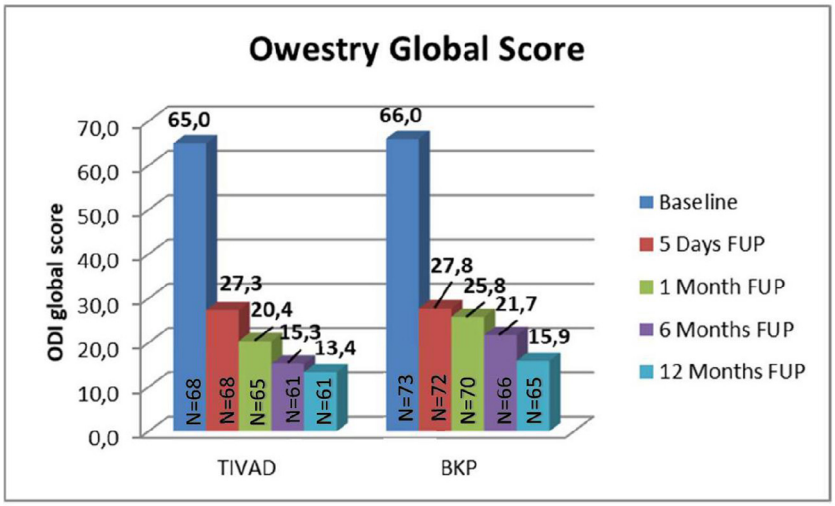
The safety profile was satisfactory for both procedures with similar proportions of VCFs with cement extravasation outside of the treated VB (47.3% for TIVAD, 41.0% for BKP; p=0.436). Extravasations into the adjacent intervertebral discs (superior, inferior, and both discs) were also evaluated. A detailed analysis with respect to the different locations can be taken from Table 6. No symptomatic cement leakage was reported. In comparison with the TIVAD technique, BKP was observed to have a rate of adjacent fractures more than double (27.3% vs. 12.9%; p=0.043), and a rate of non-adjacent subsequent thoracic vertebral fractures nearly three times higher (21.9% vs. 7.4%). No patient underwent surgical re-intervention or re-treatment at the treated level. Device deficiencies/malfunctions occurred after BKP only (2 cases of balloon rupture). However, neither impacted the procedure nor the patient's clinical outcome.

Table 5
Absolute changes from baseline in pain intensity, disability, and quality of life

		N	Mean±SD	Median	Range	p Value intergroup
Pain intensity (mm on VAS)						
5 days post-surgery	TIVAD	68	−48.9±17.1	−50.0	−80.0, −3.00	0.295
	BKP	73	−52.0±21.1	−54.0	−88.0, 20.0	(Wilcoxon)
1 month post-surgery	TIVAD	65	−56.4±20.3	−60.0	−90.0, 0.00	**0.029**
	BKP	70	−47.8±25.7	−53.5	−100.0, 14.0	(Wilcoxon)
6 months post-surgery	TIVAD	61	−61.4±18.4	−67.0	−90.0, 2.0	**0.021**
	BKP	67	−51.7±25.6	−57.0	−100.0, 30.0	(Wilcoxon)
12 months post-surgery	TIVAD	61	−62.1±23.9	−70.0	−90.0, −40.0	0.061
	BKP	65	−58.7±20.4	−62.0	−100.0, 0.00	(Wilcoxon)
ODI score						
5 days post-surgery	TIVAD	68	−37.7±18.5	−41.9	−78.4, 6.7	0.885
	BKP	72	−38.2±21.7	−40.0	−84.9, 13.3	(Student)
1 month post-surgery	TIVAD	65	−44.2±21.2	−48.2	−78.4, 6.7	0.321
	BKP	70	−39.9±23.7	−42.2	−82.2, 37.8	(Wilcoxon)
6 months post-surgery	TIVAD	61	−48.3±19.0	−52.4	−85.1, −4.4	0.173
	BKP	66	−43.2±22.3	−42.2	−87.1, 24.4	(Student)
12 months post-surgery	TIVAD	61	−51.1±20.3	−53.3	−89.6, 22.2	0.513
	BKP	65	−49.2±20.4	−53.3	−91.1, −4.4	(Wilcoxon)
EQ-5D index score						
1 month post-surgery	TIVAD	65	0.45±0.29	0.50	−0.39, 1.03	0.598
	BKP	70	0.42±0.29	0.45	−0.22, 1.04	(Student)
6 months post-surgery	TIVAD	61	0.50±0.26	0.51	−0.20, 1.03	0.742
	BKP	66	0.48±0.27	0.49	−0.21, 1.03	(Student)
12 months post-surgery	TIVAD	61	0.53±0.29	0.57	−0.51, 1.03	0.641
	BKP	65	0.52±0.26	0.52	−0.0, 1.03	(Wilcoxon)

TIVAD, titanium implantable vertebral augmentation device; BKP, balloon kyphoplasty; VAS, visual analogue scale; ODI, Oswestry disability index; EQ-5D, EuroQol 5-domain questionnaire. Bolded values indicate statistical significance to $p < 0.05$.





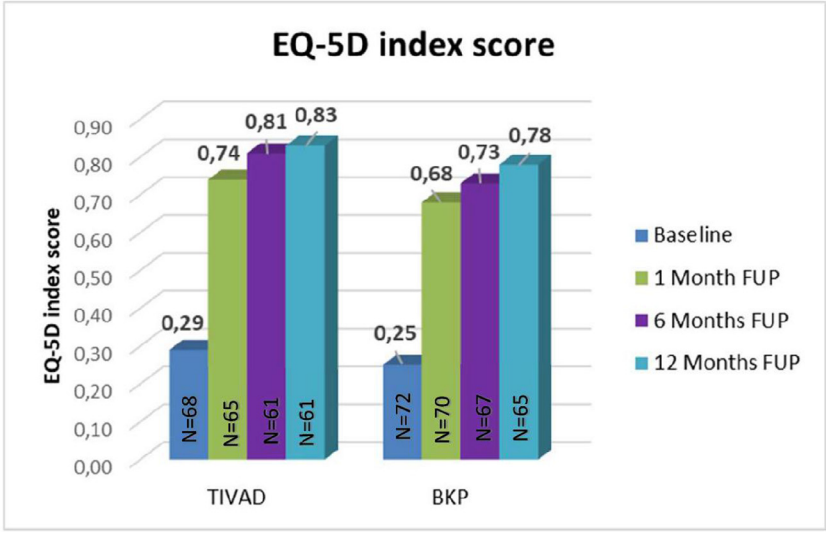


Fig. 3. Mean pain intensity, ODI score, and EQ-5D index score at each visit. Number of patients are displayed in the columns of histograms. TIVAD, implantable titanium vertebral augmentation device; BKP, balloon kyphoplasty; FUP, follow-up; ODI, Oswestry Disability Index; EQ-5D, EuroQol 5-domain questionnaire.

Table 6
Proportion of VCFs with cement extravasation and location of leakage at D5

		TIVAD N=75 vertebrae	BKP N=80 vertebrae
Cement extravasation	N	74	78
	Missing data	1	2
	NO	39 (52.7%)	46 (59.0%)
	YES	35 (47.3%)	32 (41.0%)
	Between-group test		0.436 (Chi-square)
Yeom Zone I	N	35	32
	Missing data	0	0
	NO	26 (74.3%)	32 (100.0%)
	Not assessable	3 (8.6%)	0
	YES	6 (17.1%)	0
Yeom Zone II	N	35	32
	Missing data	0	0
	NO	20 (57.1%)	27 (84.4%)
	Not assessable	1 (2.9%)	0
	YES	14 (40.0%)	5 (15.6%)
Yeom Zone III	N	35	32
	Missing data	0	0
	NO	25 (71.4%)	31 (96.9%)
	Not assessable	7 (20.0%)	1 (3.1%)
	YES	3 (8.6%)	0
Yeom Zone IV	N	35	32
	Missing data	0	0
	NO	17 (48.6%)	26 (81.3%)
	Not assessable	1 (2.9%)	0
	YES	17 (48.6%)	6 (18.8%)
Cement in disc	N	35	32
	Missing data	0	0
	Both	1 (2.9%)	1 (3.1%)
	Inferior disc	5 (14.3%)	7 (21.9%)
	NO	13 (37.1%)	8 (25.0%)
	Superior disc	16 (45.7%)	16 (50.0%)

TIVAD, titanium implantable vertebral augmentation device; BKP, balloon kyphoplasty.
In a few cases, the assessment was not possible ("not assessable") due to inferior image quality (strong out of plane and/or low image contrast).

Safety results are detailed in Table 7. Two deaths related neither to the device nor to the procedure were reported in the TIVAD group. One sudden death was due to cardiac disorder, and the other death who occurred 11 months after surgery was related to comorbidities of lung cancer and aortic aneurysm.

The list of all AEs and SAEs by body system is available online. The most common AEs reported over the study were back pain (11.8% with TIVAD, 9.6% with BKP), new lumbar vertebral fractures (11.8% with TIVAD, 12.3% with BKP), and new thoracic vertebral fractures (the latter with an incidence three times higher after BKP—21.9%—than after TIVAD procedure—7.4%). The most frequent SAEs were lumbar vertebral fractures (8.8% with TIVAD; 6.8% with BKP) and thoracic vertebral fractures (5.9% with TIVAD; 9.6% with BKP).

Discussion

In this study, Bayesian analysis demonstrated non-inferiority of the TIVAD to the predicate BKP. The SAKOS study met the criteria for study success with a posterior probability of 0.9969, which was greater than the predefined threshold of 0.987. At 12 months postsurgery, a significantly higher responder rate was shown with TIVAD compared to BKP (89.8% vs. 87.3%; p=0.0016). Results further established superiority of TIVAD to BKP with respect to overall success, the additional composite endpoint of success with freedom from adjacent fracture, and midline VB height restoration. Post-surgery kyphotic angle correction was similar between treatment groups. Both procedures displayed a good safety profile and allowed substantial and sustained improvement in pain, disability, and quality of life. Nevertheless, SAKOS study results suggested an advantage of TIVAD over BKP for pain relief, while significantly lower incidences of adjacent fractures, non-adjacent subsequent thoracic fractures, and osteolysis/osteonecrosis were reported with this device. These results support previous findings from a monocenter, randomized, 1-year study indicating that the TIVAD procedure had a higher potential for vertebral body height restoration and maintenance over time [5].

Improvement in quality of life is one of the most important goals of orthopedic surgery. In those patients suffering

Table 7
Safety results

	TIVAD N=68	BKP N=73	p Value
Adverse events			
At least one AE	28/68 (41.2%)	33/73 (45.2%)	
At least one serious AE*	17/68 (25.0%)	13/73 (17.8%)	
At least one AE related to procedure†	1/68 (1.5%)	5/73 (6.8%)	
At least one adverse device effect (ADE)	–	2/73 (2.7%)	
At least one serious ADE (SADE)	–	–	
At least one unanticipated SADE (USADE)	–	–	
Cement extravasation‡			
Asymptomatic leakages	34/67 (50.7%)	32/71 (45.1%)	0.505 (Chi-square)
Symptomatic leakages	None	none	
Adjacent vertebral fractures‡			
☐ Until month 6	6/64 (9.4%)	17/68 (25.0%)	**0.018** (Chi-square)
Number of fractures	9	23	
	3 patients with 2 fractures	3 patients with 2 fractures; 1 patient with 4 fractures	
☐ Until month 12	8/62 (12.9%)	18/66 (27.3%)	**0.043** (Chi-square)
Number of fractures	12	26	
	2 patients with 2 fractures; 1 patient with 3 fractures	3 patients with 2 fractures; 1 patient with 3 fractures; 1 patient with 4 fractures	
Subsequent vertebral fractures‡			
☐ Until month 6	4/64 (6.3%)	6/67 (9.0%)	0.745 (Fisher)
Number of fractures	6	7	
	2 patients with 2 fractures	1 patient with 2 fractures	
☐ Until month 12	6/62 (9.7%)	6/65 (9.2%)	0.931 (Chi-square)
Number of fractures	8	9	
	2 patients with 2 fractures	3 patients with 2 fractures	
Device/cement bolus migration (surgery not required)	1/68 (1.5%)	3/73 (4.2%)	
Osteolysis-osteonecrosis‡			
☐ Until month 1	1/61 (1.6%)	8/63 (12.7%)	**0.033** (Fisher)
☐ Until month 6	2/61 (3.3%)	1/63 (1.6%)	0.616 (Fisher)
☐ Until month 12	2/59 (3.4%)	1/58 (1.7%)	1.000 (Fisher)

TIVAD, titanium implantable vertebral augmentation device; BKP, balloon kyphoplasty. Bolded values indicate statistical significance to $p < 0.05$.
Data are n/n (%).

* The most frequent SAEs were lumbar vertebral fractures (six patients with TIVAD; five patients with BKP) and thoracic vertebral fractures (four patients with TIVAD; seven patients with BKP).

† AEs related to procedure (non-serious events): thoracic vertebral fracture in five patients with BKP; non-serious rib fracture in one patient with TIVAD.

‡ One hundred seventeen patients had complete radiological data available for analysis.

from severe pain (defined by Collins et al. as an initial mean score over 75 mm) [20], the median reduction in VAS score obtained with both procedures was ≥50 mm. This improvement is higher than the 30-mm clinically important difference that corresponds to patients' perception of adequate pain control [21]. Moreover, median improvements from baseline in ODI score were ≥40 points, exceeding the 12.8 point minimally clinically important difference [22], and improvements of ≥0.45 points exceeded the 0.08 threshold for EQ-5D index [23].

Although the SAKOS study was performed in several European countries, it is interesting to note that the study population was very similar to what has been reported in the medical literature for large-sized US-based BKP studies [24,25]. This has been observed with regards to sex ratio (predominantly female), patient age (median: 74 years old), baseline back pain VAS and ODI. More importantly, the clinical and safety results of the SAKOS study compare favorably with those reported in the BKP literature over the 5 past years. Specifically, patients in the BKP group experienced a mean VAS improvement of 58.7 mm (5.87 cm) compared to baseline, which is consistent with the typical improvement ranging from 4 to 7 cm noted in BKP studies [24,26–30]. Improvements in ODI scores of 49.2 points at 12 months are similarly consistent with the literature, which reports an improvement range of approximately 30 to 61 points [24,25,29,30]. Extravasation rates vary considerably in the literature, since some studies only report symptomatic leaks, whereas others incorporate a systematic imaging-based review to identify all intraoperative leaks. Thus, a focus was placed upon large studies evaluating cement leakages as part of the study design. It was found that cement leakage rates for TIVAD and BKP are consistent with rates reported in these studies, which range from

approximately 48% to 78% [25,27,31–33]. Furthermore, the absence of complications associated with extravasation is also consistent with the literature.

Some have raised a concern of an increased incidence of adjacent fractures due to alterations in spine biomechanics after cement augmentation [34]. SAKOS study results showed that the incidence of adjacent fractures was significantly lower after TIVAD procedure than after BKP (12.9% vs. 27.3%; p=0.043). Such a result is promising as it is well known that each additional fracture places the patient at higher risk for morbidity and mortality.

The SAKOS study satisfied requirements issued by a recent Task Force after reviewing randomized studies comparing BKP to other interventions, namely allocation concealment, independent radiologic assessors blinded to treatment and timepoints, adequately powered sample size and responder analyses, systematic collection of radiographic data, and adverse events [9]. Moreover, the multicenter, multinational design, as well as the similarity between the study data and medical literature support generalizability of the study findings.

Another strength of this study is the use of sensitivity analyses that provide robust support for the conclusions made on the primary composite endpoint. Missing data is a common problem in large studies and statistical inferences frequently involve underlying assumptions with variable plausibility. Sensitivity analyses are recommended in order to determine the extent to which the primary results are robust to the assumptions that were made [35]. The percentage of premature withdrawals (10.6%) makes unlikely any bias to the statistical analysis.

Limitations in this study included a lack of patient blinding as well as certain study endpoints to support device clearance. VAS reduction of >20 mm or no change in ODI over 12 months may not be considered successful clinical outcomes, even though both endpoints demonstrated improvement throughout the duration of the study.

Conclusions

In summary, the SAKOS study findings support the use of the TIVAD as an early treatment option of painful, acute VCFs with an excellent risk/benefit profile. Results on the primary composite endpoint met the criteria for study success, supporting the finding of non-inferiority to BKP. Furthermore, the study results demonstrated radiographic superiority of the TIVAD over BKP with regards to freedom from adjacent level fractures and minor superiority for midline VB height restoration at 6 and 12 months.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.spinee.2019.07.009.

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