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Prospective Controlled Trial of STAR Total Ankle Replacement Versus Ankle Fusion: Initial Results

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ABSTRACT

Background: **Mobile-bearing ankle replacements have become popular outside of the United States over the past two decades. The goal of the present study was to perform a prospective evaluation of the safety and efficacy of a mobile-bearing prosthesis to treat end stage ankle arthritis. We report the results of three separate cohorts of patients: a group of Scandanavian Total Ankle Replacement (STAR) patients and a control group of ankle fusion patients (the Pivotal Study Groups) and another group of STAR total ankle patients (Continued Access Group) whose surgery was performed following the completion of enrollment in the Pivotal Study.** ***Materials and Methods:*** **The Pivotal Study design was a non-inferiority study using ankle fusion as the control. A non-randomized multi-centered design with concurrent fusion controls was used. We report the initial perioperative findings up to 24 months following surgery. For an individual patient to be considered an overall success, all of the following criteria needed to be met: a) a 40-point improvement in total Buechel-Pappas ankle score, b) no device failures, revisions, or removals, c) radiographic success, and d) no major complications. In the Pivotal Study (9/00 to 12/01), 158 ankle replacement and 66 arthrodesis procedures were performed; in the Continued Access Study (4/02 to 10/06), 448 ankle replacements were performed, of which 416 were at minimum 24 months post-surgery at time of the database closure.** ***Results:*** **Major complications and need for secondary surgical intervention were more common in the Pivotal Study arthroplasty group than the Pivotal Study ankle fusion group. In the Continued Access Group, secondary procedures performed on these arthroplasty patients decreased by half when compared with the Pivotal Arthroplasty Group. When the Pivotal Groups were compared, treatment efficacy was higher for the ankle replacement group due to improvement in functional scores. Pain relief was equivalent between fusion and replacement patients. The hypothesis of non-inferiority of ankle replacement was met for overall patient success.** ***Conclusion:*** **By 24 months, ankles treated with STAR ankle replacement (in both the Pivotal and Continued Access Groups) had better function and equivalent pain relief as ankles treated with fusion.**

Level of Evidence: II, Prospective Controlled Comparative Surgical Trial

Key Words: STAR; Ankle Replacement; Ankle Fusion

INTRODUCTION

Although primary osteoarthritis of the human ankle does occur, end-stage arthritis is more frequently the result of trauma.[43] The increasing prevalence of severe ankle injuries is postulated to be a substantial cause of the increasing incidence of patients seeking treatment for painful ankle arthritis.[6] Current US estimates for the burden of degenerative ankle disease suggests greater than 50,000 new cases are reported each year.[5] The physical disability from ankle arthritis as quantified by generic outcome scales is equivalent to that for other major medical conditions such as coronary artery disease, hemodialysis, hip arthrosis or cervical spine pain with radiculopathy.[17,44] The treatment options include ankle joint replacement arthroplasty, ankle fusion and ankle distraction arthroplasty. Each of these procedures are associated with unique concerns, and none are clearly optimal for

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all patients with debilitating ankle arthritis.

Since 1882, when Eduard Albert first described ankle arthrodesis as treatment for infantile paralysis in a 11-year-old female, this operation has become the standard treatment for ankle degeneration.[1] Successful ankle fusion is generally met with good pain relief and patient satisfaction, however, the treatment is not without its inherent limitations. The convalescence period after ankle fusion requires immobilization until there are clinical and radiographic signs of satisfactory fusion, generally averaging 12 to 20 weeks.[15,23,42,53]

A recently published systematic review of the relevant evidence suggests that approximately one in ten patients will develop a nonunion, and most of these require a revision arthrodesis procedure.[19] Those with satisfactory outcomes may have functional limitations, including difficulty negotiating uneven ground, walking up and down inclines and challenges with automobile driving.[34,36] Eventually, adjacent joints may become painful due to premature arthritis,[9,16,22,49] and require a secondary procedure;[7] two recent publications have reported results with conversion of painful ankle arthrodesis to total ankle arthroplasty.[18,21] The limitations of ankle arthrodesis (e.g. nonunion, malunion, functional impairment and eventual development of adjacent joint arthritis) and the early success of hip and knee replacement surgeries stimulated great interest in the 1970's in ankle replacements. However, initial ankle replacement designs and surgical techniques were fraught with disappointment and failure.[24,31,50] Among the factors now thought to have contributed to early failures were the use of non-anatomic or mal-constrained designs, poor cement technique, excessive bone resection and inappropriate indications.[7,10,32,40]

In the 1990's, a newer generation of implants became available for clinical use with improved medium term results. In the United States, the Agility ankle (Depuy, Inc, Warsaw, IN) was introduced.[25] It is a fixed bearing ankle replacement which permits motion at a metal-polyethylene interface at the cost of planned interface incongruity and loss of constraint. In Europe, three-part mobile bearing ankles have been popular with encouraging intermediate-term clinical reports published for the Scandinavian Total Ankle Replacement (STAR)[26–29,46,50,53–55] (Link, Inc, Hamburg, Germany), the LCS Total Ankle[13](Endotec, Inc. South Orange, NJ), the Hintegra[20] (New Deal, Lyon, France), and the Salto[4] (Tornier, Grenoble, France).

The STAR is a three-part, "mobile bearing" replacement. It is designed to permit motion at two interfaces: one above and one below the polyethylene bearing. The upper interface is a flat planar surface, permitting internal and external rotation as well as translation in the antero-posterior and medial-lateral directions. The inferior articulating surface is shaped like a cylinder, allowing plantarflexion-dorsiflexion motion. The combined potential of the two articulating surfaces is to allow a moving axis of motion that theoretically reduces shear stresses at the bone-implant interfaces, thus promoting fixation and long term stability of the implant.

The United States Food and Drug Administration (FDA) considers all mobile bearing joint replacements as class III "experimental" designs. The FDA's Office of Device Evaluation permits the use of standard mobile bearing ankle replacements only with an approved Investigational Device Exemption (IDE). The goal of the present IDE study was to perform a 2-year prospective, non-randomized comparison of the safety and efficacy of the mobile-bearing STAR prosthesis to ankle fusion in the evaluation of the treatment of end stage ankle arthritis. The hypothesis was that overall success of the ankle replacement surgery was not inferior to that of ankle fusion.

MATERIALS AND METHODS

Study design

This study was designed to evaluate the safety and efficacy of the STAR to treat ankle arthritis, and approved as part of the investigation device exemption (IDE) by the Food and Drug Administration (FDA). The Pivotal Study design was a non-inferiority study using ankle fusion as the control. A randomized approach was not used because of concerns about achieving adequate patient accrual. Rather, a non-randomized design with concurrent controls was employed. The first phase (Pivotal Study), included patients treated with either the STAR group (enrolled between September 2000 and December 2001) or a concurrent ankle fusion control group (enrolled between Sept 2000 and April 2005). In this study, 158 STAR ankles were implanted at ten different sites (12 surgeons) and 66 ankle fusions (the control subjects) were performed at five other institutions (five surgeons). The second phase of the study included a Continued Access Group of 448 patients (enrolled between March 2002 and October 2006) treated only with the STAR ankle at the same ten institutions that were involved with the STAR ankle treatment during the Pivotal Study. The clinical sites, investigators, and treatment subgroup that participated in the study are summarized in Table 1. The same inclusion/exclusion criteria were used at all institutions for either arthroplasty or arthrodesis procedures. The separate case series from these centers were combined for purposes of the analysis.

The selection criterion for the STAR ankle investigators included foot and ankle orthopaedic surgeons who had considerable experience with ankle fusion surgery and were willing to enroll patients in a trial of a novel implant design with a favorable initial European record for safety and efficacy. At the commencement of the study, these surgeons, at best, had very limited experience with either the anterior approach to the ankle joint, or implantation of total ankle components. In an effort to make it difficult to "cherry pick" cases for both subgroups in the study, we identified investigators that were willing to limit the choice of TAR treatment to a STAR, and not use other ankle implants. For the arthrodesis subgroup, we enlisted surgeons who had

Table 1: Listing of site and principal investigators for each treatment group

Site	Principal Investigator	Treatment Group
RAMann MD INC, Oakland, CA	Roger A Mann MD	STAR Ankle
St. Alphonsus Reg Med Center, ID	Michael J. Coughlin, MD	STAR Ankle
Univ. of Iowa, Orthopedic Surgery, IA	Charles Saltzman, MD	STAR Ankle
Univ. Texas Medical School, TX	Thomas Clanton, MD	STAR Ankle
Mayo Clinic—Jacksonville, FL	James DeOrio, MD	STAR Ankle
Orthopaedic Foot & Ankle Center, OH	Thomas Lee, MD	STAR Ankle
Kansas Univ. Medical Center, KS	Greg Horton, MD	STAR Ankle
Florida Orthopaedic Institute, FL	Arthur Walling, MD	STAR Ankle
Baylor University Medical Ctr, TX	James Brodsky, MD	STAR Ankle
Duke Univ. Medical Center, NC	James Nunley, MD	STAR Ankle
USC School of Medicine, CA	David Thordarson, MD	Control
Hospital for Special Surgery, NY	Jonathan Deland, MD	Control
Stanford Univ. Medical Center, CA	Loretta Chou, MD	Control
Extreme Orthopaedics, PA	Keith Wapner, MD	Control
Miller Orthopaedic Clinic, NC	Robert Anderson, MD	Control

substantial experience in performing ankle arthrodeses, and were willing to enroll patients with the standardized operative technique as defined in the clinical protocol.

After initiation of the study in the United States, STAR implants were only performed within the study. After the FDA reviewed initial safety data from the Pivotal Study at the ten ankle replacement centers, a controlled number of patients had STAR ankles implanted in a Continued Access Study. Patients who had bilateral procedures were evaluated for safety only.

Study population

Institutional Review Board study approval was obtained at each study site. All consecutive subjects meeting the eligibility criteria, agreeing to participate in the study, and giving informed consent were enrolled in the study. During the study period, no patient was able to have this replacement surgery outside of the study. The following lists the inclusion and exclusion criteria for the patient enrollment for both the arthroplasty and fusion groups in the Pivotal Study.

Inclusion criteria

- Moderate or severe pain, loss of mobility and function of the involved ankle (Buechel-Pappas Scale total score of less than 50 and Buechel- Pappas pain score of 20 or less)
- Primary arthrosis, post traumatic arthrosis or rheumatoid arthrosis
- Having completed at least six months of conservative treatment, confirmed by the patient medical history, radiographic studies and medication record.
- Willing and able to give informed consent

Exclusion criteria

- Patients who had not reached skeletal maturity
- Active or prior deep infection in the ankle joint or adjacent bones
- Prior arthrodesis at the involved site
- History of mental illness or patient demonstrates that their mental capacity may interfere with their ability to follow the study protocol
- Obesity (weight greater than 250 lbs)
- History of current or prior drug abuse or alcoholism
- Any physical condition precluding major surgery
- Hindfoot malpositioned by more than 35 degrees or forefoot malalignment which would preclude a plantigrade foot
- Lower extremity vascular insufficiency demonstrated by Doppler arterial pressure
- Avascular necrosis of the talus
- Inadequate skin coverage about the ankle joint
- Severe deformity that would not normally be eligible for ankle surgery
- Prior surgery and/or injury that has adversely affected the ankle bone stock
- Severe osteoporotic or osteopenic condition or other conditions that may lead to inadequate implant fixation in the bone
- Insufficient ligament support
- Motor dysfunction due to neuromuscular impairment

Patient assessment

The primary efficacy endpoint was the Buechel-Pappas (BP) score.[7] This 100-point scale which assesses pain (40

points), function (40 points), deformity (5 points), and joint motion (15 points) was selected at the time of study design in 1998 because it had been used to record outcome from other ankle replacement surgery (Appendix 1).[8] We calculated the results with and without the inclusion of motion. The function subscale is further divided into five eight-point questions pertaining to limp, standing, walking on level ground, climbing stairs, and need for lower leg or ankle support. Patients were assessed preoperatively, and at 12 months and 24 months postoperative.

Secondary efficacy endpoints included BP subscales of function and range of motion (ROM), pain Visual Analog Scale (VAS) (100 mm scale), patient satisfaction (Coughlin rating for category scale: excellent, good, fair, poor)[11], quality of life (SF-36)[52], and medication usage.

To be considered a safety success at final followup, the ankle 1) could not have undergone a revision or removal, 2) must have had no major complications, and 3) for the arthroplasty cases demonstrated no evidence of migration or loosening of the prosthesis on radiographic analysis. Major complications were identified as wound problems, infections, non-traumatic bone fractures, implant problems and other bony changes, such as heterotopic ossification or osteolysis, that required surgical intervention as a treatment solution.

Surgical interventions were classified into 1) revision or removal of any components or hardware or 2) other interventions including a) open reduction and internal fixation of malleolar fractures, b) removal of heterotopic bone, c) treatment of a nonunion, and d) irrigation and debridement of wounds.

In this prospectively conducted and carefully monitored study all clinically significant adverse events were recorded, analyzed and reported. A list of expected adverse events related to the surgical site was detailed in the clinical protocol. However, all operative and non-operative site adverse events that resulted in either a) a new or change in treatment, or b) a new diagnosis were reported for all groups in both the Pivotal and Continued Access Studies. The specific safety endpoints of interest for both groups were any complications of surgery. For only the STAR ankle group, any device failure/removal/revision or radiographically confirmed loosening and migration were identified. For only the arthrodesis group, any non-union, malunion, delayed union, or revision was identified. Delayed unions were defined by lack of radiographic signs of fusion at 6 months. Non-union was defined as lack of fusion at 12 months.

Overall patient success for an individual patient was defined as success for both efficacy and safety. In order for a patient to be considered an overall success, they had to be rated a success in both domains (safety and efficacy).

a) A 40-point improvement in total BP score,
b) No device failures, revisions, or removals,
c) Radiographic success (defined as no radiographic evidence of loosening or migration in the Pivotal Study arthroplasty group and no radiographic evidence of non-union, delayed union, or malunion in the Pivotal Study ankle fusion group), and
d) No major complications (defined as a lack of significant infection requiring surgical intervention, no delayed wound healing requiring surgical intervention, no significant postoperative fractures of adjacent bones requiring surgical intervention, and no significant bony changes of adjacent bones requiring surgical intervention).

Surgical techniques

Arthrodesis

The ankle arthrodesis procedures were performed through a lateral approach to the ankle joint.[45] The distal fibula was either removed or partially decorticated and placed back on as an on-lay graft. Either a cut was made in the distal tibia which was perpendicular to the long axis of the tibia, or the surfaces were prepared congruently. Care was taken not to remove the medial malleolus. The foot was placed into a plantigrade position and, when appropriate, a cut was made in the superior aspect of the talus parallel to the original cut made in the tibia. The alignment of the foot was then checked and, if satisfactory, internal fixation was applied. In general, two to three large cannulated screws placed were utilized for fixation. On-lay distal fibular grafts were fixed with small or large fragment screws and plates, when required.

Following surgery, the leg was routinely immobilized in a below-knee nonweightbearing cast for 6 weeks, then in a below-knee walking cast for 6 more weeks, followed by progressive weightbearing in a removable walking boot. The surgeon was allowed to modify the weightbearing status depending on the patient's recovery, bone stock, and signs of healing.

Ankle replacement surgery

The STAR arthroplasty procedures[12,33] were carried out through an anterior approach to the ankle joint. A 15- to 20-cm approach was made to the joint through the extensor retinaculum just over the extensor hallucis longus tendon. A combined tibial alignment guide and cutting block jig was utilized to remove the distal 5 to 8 mm of the tibia in such a way as to remove the remaining articular surface at the dome of the tibial plafond. Utilizing an additional portion of the tibial jig, a talar cutting block was utilized to remove the 4 to 6 mm of the superior dome of the talus while the foot was held in a plantigrade position. These initial cuts were all flat cuts in the axial plane.

Following this, the tibial alignment guide and cutting block were removed and a side cutting talar guide was applied and the medial and lateral 2 to 3 mm of talus was resected. A second talar cutting guide was applied and fixed to the talus. Anterior and posterior chamfer cuts were made and

these fragments were removed creating a truncated pyramidal shaped surface for seating of the talar component. A vertical slot was created in the central aspect of the talus to receive the fin of the talar prosthesis. The talar prosthesis of correct size was then placed onto the talus, and impacted onto the prepared talar surface.

Returning to the distal tibia, the tibial alignment and cutting block jig was reapplied, and two cylindrical holes were drilled from anterior to posterior at the edge of the prepared distal tibial surface to accommodate the barrels of the tibial component. A gouge was then used to connect the holes with the prepared flat surface of the distal tibia. A tibial component of the correct size was then inserted. A polyethylene trial spacer of appropriate size was placed between the tibial and talar components and a permanent spacer was then selected and inserted based on the trial size.

The lower leg and ankle were then immobilized in a below knee cast for a period of 6 weeks following the arthroplasty. The general protocol was minimal weightbearing during the first 2 weeks, 50% weightbearing for the next 2 weeks, and then full weightbearing in a cast for the next 2 weeks. The cast was removed at 6 weeks following surgery.

Radiographic analysis

All fusion radiographs were interpreted by the surgeon of record. The sole determination of radiographic success was either a fused ankle or non-union. CT scans were not used to confirm fusion. The status of fusion was not independently verified.

Postoperative radiographs of the ankle replacements in the Pivotal Study were collected and evaluated by a single examiner (CLS). Postoperative radiographs of the ankle replacements for the Continued Access Group were evaluated by an independent musculoskeletal radiologist after receiving training by the pivotal trial examiner (CLS) The independent radiologist was not familiar with the specific goals of the study. All images were digitized. Size, brightness and contrast were adjusted so that all the measurement points could be seen with maximum quality. The 0.5-mm wire wrapped by the manufacturer around the mobile bearing was used to normalize all distance measurement.

The radiographic analysis technique was developed prior to the study based upon the senior investigators' knowledge of cemented total ankle replacement. In these ankles migration and peri-prosthetic lucencies were early signs associated with eventual component loosening and failure. Thus, we selected these specific signs as predictors in the arthroplasty trial of clinical failure. When any of these radiographic signs were recognized the case was designated as a safety failure. As we gained more experience reading the arthroplasty radiographs within the pivotal trial, we found that signs of radiographic loosening on radiographs taken within 12 months of surgery were not particularly predictive of eventual clinical failure for this non-cemented ankle replacement. Post hoc, we conducted two "revised" analyses. Two specific circumstances resulted in revising the radiographic classification: 1) inappropriate carrying forward of radiographic information, and 2) inappropriate interpretation of radiographic findings as predictive of clinical failures.

Parameters measured

The following six parameters were measured and used to evaluate subsidence or migration of the total ankle prosthesis:

1. Joint space height
2. AP position of the talus
3. Height of the talus
4. Angle A—the lateral tibial component angle
5. Angle B—the lateral talar component angle
6. Angle C—the AP/mortise tibial component angle

For a detailed description of how these parameters were each measured, see Appendix 2 as well as Figures 1 and 2.

Based on a previous study, we used the following criteria for radiographic measurement[39]:

1) Tibial or talar component migration was classified as 0, 0 to 4 mm, and more than 4 mm on both lateral and AP/mortise views. We used the diameter of the wire around the mobile bearing as a magnification adjusted indicator for linear distance (0.5 mm).
2) Tilting (either varus/valgus or plantarflexion/dorsiflexion) for each component was expressed as 0, 0 to 4 mm, and more than 4 mm on the AP/mortise view.
3) Radiolucencies (around each component were evaluated on all views available) the size (0, 0 to 4 mm, and more than 4 mm) and location of this region were noted.

A priori, the presence of any of these findings were considered radiographic failure: tibial or talar component migration more than 4 mm, tibial or talar component tilting more than 4 mm; presence of a radiolucency more than 4 mm.

Statistical methods

Selection of statistical tests

The raw proportion of patients meeting the criterion of a 40-point increase in total BP score was compared between groups using a chi-square test. The primary efficacy endpoint of mean total BP score was compared between the two treatment groups using the method of Blackwelder[3] to determine if the overall outcome was equivalent between the two groups. It was based upon a t-score (standard comparison) and these were evaluated to the primary efficacy endpoint. In addition, based on previous methodology,[14,35] a two-sample t-test was performed, without adjustment for multiple comparisons because the analysis was performed at one time-point.

The secondary endpoints of pain VAS and quality of life were each compared between treatment groups using a two-sample t-test. The secondary endpoints of function and range of motion BP subscale scores and patient satisfaction were compared between treatment groups using non-parametric tests. Finally, the raw proportion of subjects experiencing each type of adverse event was compared using chi-square tests or Fisher's exact test as appropriate.

Sample size calculation for pivotal study

Appendix 3 details the methods for the sample size calculation. The sample size was calculated separately for the primary efficacy endpoint and the primary safety endpoint. Since the study was not originally designed to include the composite overall success a required sample size was not calculated for this composite result. Additionally, all sample size calculations were developed based upon a 2:1 ratio of the Pivotal Study arthroplasty group to the ankle fusion group.

The sample size required to evaluate the primary efficacy endpoint of equivalent BP score was 36 (12 arthrodeses and 24 STAR ankles). This sample size was based on data collected by BP and assumed that the clinically insignificant difference in the mean BP score ("delta") was 10 points. This choice of delta was appropriate, since it was only 10% of the total 100-point scale, and it was also equal to the smallest width of the categories used to classify the scale (85 to 100 = Excellent, 75 to 85 = Good, 65 to 75 = Fair, etc.). This scale was selected at the time of study design (1999) because it was originally designed to assess outcomes of total ankle replacement, and had been reported in several prior studies. Review of the previously published results using this scale helped determine the minimal clinically significant difference for efficacy success.

The sample size required to evaluate the safety endpoint was estimated to be 201 (67 arthrodeses and 134 STAR ankles). This sample size *a priori* assumed a success rate of 80% in both groups and a delta of 15% to be acceptable to demonstrate non-inferiority. Based on the safety profile of the STAR device reported pre-study, the investigators considered this to be a clinically acceptable level for the delta.

RESULTS

This report summarizes the results of the STAR experience during each of two phases in an FDA trial.

Patient population

Relevant demographics and characteristics, and etiology for ankle degeneration for the patient population are shown in Table 2. There were no significant differences in gender, race, height or weight between the Pivotal Study arthroplasty and fusion groups. The arthroplasty a) Pivotal and b) Continued Access groups were not different with respect to gender, race, age, height and weight. The Pivotal Study arthroplasty ankle patients were significantly older (63 years old) than the Pivotal Study fusion group (57 years old; $p = 0.004$).

The four subscales of the BP score were analyzed at baseline to evaluate the similarity of the patient populations (Table 3). The function component of the BP score was significantly lower (more impaired) for the Pivotal Study arthroplasty group than the fusion group and both the pain subscore and total score trended toward a significantly lower score in the STAR arthroplasty group. The Continued Access STAR arthroplasty group demonstrated similar results in the function, pain, and ROM sub-scores but significantly lower total scores and less deformity (higher score) compared to the Pivotal Study arthroplasty group.

The study's completion rates and related factors are listed in Table 4. The database was last updated August 2007 for this analysis. At that point, 25 of the 448 (5.6%) patients had not reached the 24-month followup milestone, four had died, one was considered a failure but removed from continued followup, and three were transferred to the bilateral arm of the study, yielding 415 expected Continued Access patients at 24 months. Additionally by August 2007, we were unable to schedule a 24-month followup monitoring trip to sites of 42 patients, leaving a total of 374 (90%) Continued Access patients with some data collected at 24 months. Of these Continued Access patients, 314 (76%) had a full set of BP scale data, 274 (66%) had a complete set of safety data (surgical data, radiographic data and major complication data), and 342 (82%) had 24-month followup clinical data that included all components for safety except 24-month radiographic data.

In summary, the two Pivotal Study groups (arthroplasty and fusion) were similar in gender, race, height, and weight. However, the arthroplasty group was more debilitated as evidenced by higher pain and lower function scores, a greater percentage had rheumatoid arthritis, and, on average, this group was 6 years older. The patients in the Continued Access STAR arthroplasty group demonstrated generally similar characteristics to the Pivotal STAR arthroplasty group.

Operative characteristics

All of the operative variables were equivalent between the two groups in the Pivotal Study (arthroplasty vs fusion): [1] operative time, $p = 0.613$; [2] anesthesia time, $p = 0.784$; [3] estimated blood loss, $p = 0.318$; and [4] length of stay, $p = 0.810$.

Perioperative adverse events

Detailed review of all reported adverse events (AEs) in the Pivotal Study indicated some events that occurred either during the procedure or prior to discharge and were more common in the arthroplasty group than the arthrodesis group. These events were primarily related to the anterior ankle surgical approach or the technical aspects of component implantation. Indeed, in the case of malleolar fractures,

Table 2a: Baseline demographics for each treatment group, mean (standard deviation)

Demographic Description	Pivotal STAR (N = 158)	Pivotal Fusion (N = 66)	*p* value	Continued Access STAR (N = 435)	*p* value*	Combined STAR (N = 593)
Age (years)	63.2 (12.6)	57.1 (12.3)	0.004	63.0 (11.6)	0.850	63.1 (11.9)
Height (inches)	67.3 (3.7)	67.0 (4.5)	0.612	66.8 (3.9)	0.150	66.9 (3.85)
Weight (lbs)	180.9 (34.9)	185.6 (38.6)	0.378	180.7 (35.2)	0.943	180.8 (35.1)
Gender						
Male	78 (49.4%)	30 (45.5%)	0.593	179 (41.1%)	0.074	257 (43.3%)
Female	80 (50.6%)	36 (54.5%)		256 (58.9%)		336 (56.7%)
Race						
Caucasian	152 (96.2%)	60 (90.9%)	0.205	418 (96.1%)	0.940	570 (96.1%)
African American	4 (2.5%)	2 (3%)		6 (1.4%)		10 (1.7%)
Hispanic	1 (0.6%)	3 (4.5%)		7 (1.6%)		8 (1.4%)
Other	1 (0.6%)	1 (1.5%)		4 (0.9%)		5 (0.8%)

*, Comparison of the STAR groups from the Pivotal and Continued Access studies

Table 2b: Primary diagnosis for each treatment group

Primary Diagnosis	Pivotal STAR (N = 158)	Pivotal Fusion (N = 66)	*p* value	Continued Access STAR (N = 435)	Combined STAR (N = 593)
Primary Arthritis	62 (39.2%)	19 (28.8%)	0.054	95 (21.8%)	157 (26.5%)
Post-Traumatic Arthritis	76 (48.1%)	43 (65.2%)		269 (61.8%)	345 (58.2%)
Rheumatoid Arthritis	20 (12.7%)	4 (6.5%)		31 (7.1%)	51 (8.6%)
Metabolic Disorder	NA	NA	NA	40 (9.2%)	40 (6.7%)

Table 3: Baseline BP subscale scores for each treatment group, mean (standard deviation)

Subscale	Pivotal STAR (N = 158)	Pivotal Fusion (N = 66)	*p* value	Continued Access STAR (N = 435)	*p* value*	Combined STAR
Deformity	2.8 (1.3)	2.9 (1)	0.441	3.7 (1.1)	0.001	3.5 (1.2)
Function	18.6 (5.7)	21.1 (6.1)	0.005	15.6 (5.9)	0.596	16.4 (6.1)
Pain	10.6 (3.9)	12 (5)	0.056	9.4 (3.3)	0.174	9.7 (3.5)
ROM	8.7 (3.6)	7 (4)	0.002	8.8 (3.6)	0.773	8.8 (3.6)
Total	40.8 (7.4)	43 (8.8)	0.058	37.6 (8.5)	0.043	38.4 (8.4)

*, Comparison of the STAR groups from the Pivotal and Continued Access studies

the differences do not lend to an easy adverse event rate comparison because of intrinsic differences in the surgical technique. In the Pivotal Study arthroplasty group, 9.5% (15/158) of cases were associated with an intra-operative fracture, mostly of the malleoli. These fractures were of little consequence to the patient as they were stabilized during the initial operative procedure and healed within the time period of ankle immobilization following the total ankle surgery (6 weeks). The Continued Access Group had a nonsignificant lower rate of intraoperative fractures than the pivotal subgroup 9.5% (15/158) versus 4.8% (21/435), $p < 0.059$.

Another adverse event reported in the Pivotal Study arthoplasty group, but not the arthrodesis group, was intra-operative nerve injury (5.7% or 9/158). Seven of these adverse neurological events were transitory and resolved

Table 4: Data accounting at 24-month followup for enrolled patients in all treatment arms

# of Patients by Description	Pivotal STAR	Pivotal Fusion	Continued Access STAR		Combined STAR	
Enrolled	158	66	448		606	
Deaths	4	1	4		8	
Transferred to Bilateral Arm	4	0	3		7	
Device Removal and Removed from Followup	2	0	1		3	
Not Out of Window at Time of Database Closure	0	0	25		25	
Expected	148	65	415		563	
Actual						
Efficacy	142	47	314	314	456	456
Safety	142	52	274*	342**	416*	484**
Overall Followup %	95.9	78.5	66.7*	82.2**	74.4*	85.8**

Followup rate with data available at the time of database closure; at the time of database closure 42 available 24-month visits for the CA subgroup remained uncollected due to access to the site for monitoring visits. *, complete set of safety data **, 24-month followup clinical data that included all components for safety except 24 month radiographic data.

with minimal or no noticeable sensory impairment. All other events reported prior to discharge occurred in less than 2% of the patient population [soft tissue edema (1.9%), decreased ROM (1.9%), and wound problems (1.3%).]

The total number of reported adverse events at the operative site by 24-month followup in the Pivotal Study was more common in the arthroplasty group compared to the fusion group. Table 5 provides a listing and frequency of each of the most common adverse events reported in the study for each of the treatment groups. In the Pivotal Study, pain ($p = 0.510$), soft tissue edema ($p = 0.076$) and infection ($p = 0.464$) were comparable in both groups. Some adverse events generally did not have substantial clinical consequences or long-term sequelae. Nerve injury was usually described as numbness on the medial aspect of the talo-navicular joint region, a consequence of neurapraxia or severing a small branch of the superficial peroneal nerve as a consequence of the anterior ankle approach. The incidence of adverse events in the Continued Access group was significantly less compared with the Pivotal Study arthroplasy group ($p = 0.007$) and, specifically, for the following classes of adverse events: pain ($p = 0.001$), soft tissue edema ($p = 0.001$), decreased ROM ($p = 0.001$), and bony changes (p value $=0.047$). No amputations were required in the Pivotal Study; one ankle replacement in the Continued Access group became infected and ultimately required a below knee amputation (this patient did not complete the study followup but was considered a safety and overall failure for the study).

Safety

Table 6 summarizes the major complication rates for each treatment group through the 24-month followup. The events that were identified as major complications related largely to the anterior surgical approach and the articulating nature of the prosthetic device. Of note, for the fusion group neither delayed union nor malunion were included in the *a priori* definition of a major complication in the study, perhaps biasing the safety results against the STAR arthroplasty group. No significant differences in major complications were seen between the Pivotal and the Continued Access groups.

Table 7 summarizes the surgical intervention rates by category for each treatment group through the 24-month period of followup. Overall, 63 (10.6%) ankle replacement patients required a secondary procedure at a minimum of 2 years followup. Notably, only two nonunions requiring treatment were reported in the control subgroup. We found a 50% decrease in the rate of patients requiring secondary surgical interventions for the Continued Access arthroplasty group versus the Pivotal Study arthroplasty group ($p = 0.001$).

Results of the radiographic analyses are presented alongside those of the initial analysis in Table 8A. In our initial analysis, we identified 8 patients with peri-implant lucencies that were initially carried forward as radiographic failures. Seven of these were clinical successes and had 24 month radiographs that showed solid, peri-implant bone in-growth. In the Revised Analysis #1 we considered these safety successes. We also found that minor settling (generally less than or equal to 5 mm) of the implant into bone during the first 12 months was not predictive of long-term clinical outcomes. In five cases, the initial settling of an implant stabilized after 12 months and showed no further change in radiographic appearance at 48 months. All five were associated with clinically satisfactory outcomes and were considered safety successes in the Revised Analysis #2. Both the initial and revised radiographic analyses and the impact on the overall success results are presented in Table 8A.

Table 5: Listing of occurrence of most common operative site adverse events by treatment group through 24-month followup

Operative Site Adverse Event	Pivotal STAR (N = 158)	Pivotal Fusion (N = 66)	*p* value	Continued Access STAR (N = 435)	*p* value*	Combined STAR (N = 593)
Pain	69 (43.7%)	32 (48.5%)	0.510	149 (34.3%)	0.001	218 (36.8%)
Nerve Injury	32 (20.3%)	5 (7.6%)	0.026	98 (22.5%)	0.775	130 (21.9%)
Bone Fracture	28 (17.7%)	2 (3.0%)	0.004	52 (11.9%)	0.061	80 (13.5%)
Soft Tissue Edema	25 (15.8%)	4 (6.1%)	0.076	22 (5.1%)	0.001	47 (7.9%)
Decreased ROM	10 (6.3%)	Expected	NA	3 (0.7%)	0.001	13 (2.2%)
Wound Problem	32 (20.3%)	4 (6.1%)	0.011	92 (21.1%)	0.983	124 (20.9%)
Infection	7 (4.4%)	5 (7.6%)	0.464	20 (4.6%)	0.536	27 (4.5%)
Bony Changes	12 (7.6%)	NA	NA	21 (4.8%)	0.047	33 (5.6%)

*, Comparison of the STAR groups from the Pivotal and Continued Access studies

Table 6: Summary of major complications by treatment group through 24-month followup

Major Complication Classification	Pivotal STAR (N = 158)	Control (N = 66)	*p* value	Continued Access STAR (N = 435)	*p* value*	Combined STAR (N = 593)
Any Major Complication	14 (8.9%)	1 (1.5%)	0.045	23 (5.3%)	0.087	37 (6.2%)
Wound Problems	5 (3.2%)	1 (1.5%)	0.487	7 (1.6%)	0.235	12 (2.0%)
Infection	2 (1.3%)	1 (1.5%)	0.883	5 (1.1%)	0.710	7 (1.2%)
Bone Problems	8 (5.1%)		0.063	13 (3.0%)	0.227	21 (3.5%)
Wound Problems and Infection	1 (0.6%)		0.518		0.097	1 (0.2%)

*, Comparison of the **STAR** groups from the Pivotal and Continued Access studies

The components of safety success are further reported in Table 8B.

Efficacy

The mean improvement in each of the BP subscales, including individual components for the function subscale, at 24-months followup was recorded for both treatment groups in the Pivotal Study (Table 9). The STAR arthroplasty group improved significantly greater than the fusion group in all subscales except for pain relief, walking and presence of a limp. Total score improvement was 50% greater for the arthroplasty group vs. the fusion group (40 versus 26). Additionally, a 40-point improvement in total score was defined as the efficacy endpoint for the Pivotal Study; the arthroplasty group had a mean improvement of 40 points and the fusion group had a mean of 26 points improvement at 24-months followup, $p < 0.001$.

The other efficacy measures demonstrated equivalent results between the two groups in the Pivotal Study at 24-months followup. First, the pain visual analog scale (100 mm) demonstrated a non-statistically different improvement in pain for the arthroplasty group (51.8 points) compared with the fusion group (44.6 points) ($p = 0.089$). Table 10 summarizes the pain VAS findings. Similarly, equivalent results were reflected by the change in the 40 point pain subscale of the BP instrument with a mean reduction of 21.5 and 19.2 points ($p = 0.14$), respectively. Secondly, patient satisfaction was high with approximately 85% of the patient population in both groups reporting good to excellent results (STAR: 123/144 or 85.4% and control subgroup: 38/45 or 84.4%).

Overall success rates

Table 7 summarizes the success rates for each treatment group. The 15% delta was defined for the study as the threshold to determine equivalence between treatment groups for the safety analysis. In the Pivotal Study, the arthroplasty group demonstrated significantly greater efficacy ($p < 0.001$) and overall success compared to the fusion group at 24-month followup.

DISCUSSION

In this prospective study comparing ankle replacement

Table 7: Summary of surgical interventions by treatment group through 24-month followup

	Pivotal STAR (N = 158)	Pivotal Fusion (N = 66)	*p* value	Continued Access STAR (N = 435)	*p* value*	Combined STAR (N = 593)
# of Patients with Interventions	26 (16.5%)	7 (10.6%)	0.219	37 (8.5%)	0.001	63 (10.6%)
Intervention Type						
Revision, Removal	12 (7.6%)	7 (10.6%)	0.833	16 (3.7%)	0.010	28 (4.7%)
Other Intervention	18 (11.4%)	1 (1.5%)	0.016	23 (5.3%)	0.007	41 (6.9%)

*, Comparison of the STAR groups from the Pivotal and Continued Access studies

Table 8a: Success rates at 24-months followup for all treatment groups

Success Category	Pivotal STAR		Pivotal Fusion			Continued Access STAR		Combined STAR	
	n/N	%	n/N	%	*p* value	n/N	%	n/N	%
Efficacy (BP ⩾40 point improvement)	83/142	58.5	7/47	14.9	<0.001	239/314	76.1	322/456	70.6
Safety—Initial	101/142	71.1	43/52	82.7	0.1668	233/274	85.0	334/416	80.3
Combined Safety—No Carrying Forward of Early Radiographic Findings	108/142	76.1	43/52	82.7	0.4497	233/274	85.0	341/416	82.0
Combined Safety—Radiographic Findings Not Predictive of Clinical Failure	113/142	79.6	43/52	82.7	0.7905*	233/274	85.0	346/416	83.2
Overall Success–Initial	64/142	45.1	7/51	13.7	<0.001	172/277	62.1	236/419	56.3
Overall—No Carrying Forward of Early Radiographic Findings	68/142	47.9	7/51	13.7	<0.001	172/277	62.1	240/419	57.3
Overall—Radiographic Findings Not Predictive of Clinical Failure	70/142	49.3	7/51	13.7	<0.001	172/277	62.1	242/419	57.8

* Only Safety Success category in which the 15% Delta was satisfied

to ankle fusion, at 24 months followup, treatment efficacy was improved or equivalent in the arthroplasty arm compared with the fusion arm, depending on outcome variable measured. The Pivotal Study was designed as a 24-month non-inferiority study; the ankle replacement group satisfied or exceeded those criteria for all efficacy outcome variables. By design, the study scrutinized the arthroplasty patients more closely, both in the review of radiographs and in the recording of adverse events. Many of the recorded adverse events were inconsequential (malleolar fracture, numbness, postoperative swelling, diminished post- operative range of motion, postoperative pain). In the Pivotal Study, the arthroplasty group had a higher rate of perioperative complications and adverse events, several of which decreased in the Continued Access study; the rate of secondary surgical procedures decreased by 50% in the Continued Access group. The potential long-term advantages of ankle replacement, including sustained functional benefits, options for revision and reduced incidence of secondary hindfoot arthritis were not evaluated in this study.

Table 8b: Components of safety success at 24-months followup for all treatment groups

Success Category	Pivotal STAR		Pivotal Fusion			Continued Access STAR		Combined STAR	
	n/N	%	n/N	%	*p* value	n/N	%	n/N	%
Safety Components									
No Revisions or Removals	122/142	85.9	47/52	90.4	0.5803	320/342	93.6	442/484	91.3
No Major Complications	128/142	90.1	51/52	98.1	0.1399	319/342	93.3	447/484	92.4
Radiographic Analysis									
Initial	117/138	84.8	46/52	88.5	0.6787	260/267	97.4	377/405	93.1
No Carrying Forward of Early Radiographic Findings	124/137	90.5	46/52	88.5	0.8966	260/267	97.4	384/404	95.1
Radiographic Findings Not Predictive of Clinical Failure	129/137	94.2	46/52	88.5	0.3274	260/267	97.4	389/404	96.3

Table 9: Improvement in BP scores by treatment group at 24 months, mean (standard deviation)

Subscale	Pivotal STAR ($n = 143$)	Pivotal Fusion ($N = 48$)	*p* value	Continued Access STAR ($n = 314$)	Combined STAR
Deformity	1.9 (113)	0.4 (1.2)	<0.001	0.9 (1.2)	1.2 (1.3)
Function	13.4 (7.3)	9.7 (8.7)	0.004	17.9 (7.2)	16.6 (7.6)
Stairs	1.6 (2.1)	0.9 (2)	0.039	2.5 (2.2)	2.1 (2.4)
Standing	3.4 (2.8)	1.7 (3.3)	<0.001	4.2 (2.6)	2.8 (2.5)
Support	1.7 (2.2)	0.8 (1.9)	0.016	2.3 (2.4)	3.1 (2.3)
Walking	2.6 (1.9)	2.7 (1.9)	0.746	3.7 (2.0)	3.7 (2.5)
Limp	4.1 (2.2)	3.4 (3.4)	0.114	5.2 (1.9)	4.9 (2.1)
Pain	21.5 (9.6)	19.2 (9.4)	0.14	24.2 (7.5)	23.2 (8.3)
ROM	3.6 (3.7)	−3.7 (5.1)	<0.001	3.7 (3.5)	3.7 (3.6)
Total	40.5 (15.1)	26.3 (17.1)	<0.001	46.7 (13.0)	44.8 (13.9)
Total (no ROM)	36.9 (14.5)	30.0 (15.8)	0.006	43.0 (12.3)	41.1 (13.3)

A major strength of this multi-center clinical trial was the prospective design of the study. Detailed information was recorded on every event and meticulous records were maintained and verified by an outside medical monitor. In the initial Pivotal Study, 158 arthroplasty and 68 ankle arthrodesis patients were followed. At 24-months followup, 97% of arthroplasty and 77% of arthrodesis patients completed the study. We believe that the extensive study requirements for the fusion control group, a group that received standard conventional treatment, may have contributed to the lower followup rate. These patients had little to gain by continued followup once a successful ankle fusion had been obtained. The relatively lower rate of complete followup for the Controlled Access group at 24 months (66%) reflects missing 24 month X-rays for 42 Continued Access patients; this rate increases to 82% when we include all components for safety except 24 month radiographic data.

For a number of reasons, including surgeon preference, ability to recruit and retain subjects and ethical concerns, we did not conduct a randomized controlled trial, but rather conducted a trial that assigned treatment based on study site. A disadvantage of the non-randomized design was that the arthroplasty and arthrodesis patients were enrolled in different centers, and the groups were somewhat dissimilar. While the two groups were equivalent in height, weight, and gender, the arthroplasty patients were, on average, significantly older, had a lower preoperative functional level, a higher preoperative pain level, and had a two-fold greater incidence of rheumatoid arthritis factors which we believe biased the study in favor of the fusion group as opposed to the arthroplasty group.

Table 10: Pain VAS by treatment group, mean (standard deviation)

Visit	Pivotal STAR	Pivotal Fusion	*p* value	Continued Access STAR	Combined STAR
Pre-operative	71.1 (17)	65.8 (19)	0.073	76.5 (14.2)	75.0 (15.1)
24-month	19.5 (20)	17.9 (20)	0.607	15.8 (17.5)	16.9 (18.3)
Improvement	51.8	44.6	0.089	60.7 (21.8)	57.9 (23.7)

A further limitation of the study was a difference in experience with the two procedures by the study surgeons. At the fusion study sites, the orthopaedic surgeons had substantial experience with ankle arthrodesis, as all were highly experienced foot and ankle surgeons and ankle fusion with this approach was a common procedure in their practices. This group achieved a success rate markedly higher than that reported in the literature for ankle fusion.[19] The arthroplasty study site surgeons were similarly experienced and subspecialty-focused orthopaedic surgeons. However, many began the study with far less familiarity with the anterior surgical approach and use of the STAR ankle implant. While variables of operative time, estimated blood loss, and hospital length of stay were similar for both groups in the Pivotal Study, perioperative adverse events were markedly higher in the initial Pivotal Study arthroplasty group. The overall incidence of adverse events and need for secondary procedures diminished with improved technique and greater surgeon experience with use of the ankle replacement in the Continued Access Study.

The FDA trial required the maintenance of meticulous, detailed information on every possible adverse event including, but not limited to, perioperative pain, soft tissue edema, wound problems, nerve injury, malleolar fracture, and wound problems. Operative site adverse events occurred more frequently in the arthroplasty group. Many of these events were related to the anterior surgical approach currently used for all total ankle replacements. The anterior approach is associated with a higher rate of sensory nerve dysfunction, wound problems, and soft tissue edema than the lateral approach used in the fusion group in the study. The anterior surgical approach requires, in some cases, either retraction or transection of a medially directed terminal sensory branch of the medial branch of the superficial peroneal nerve to gain full access to the ankle joint; whereas the trans-malleolar approach for ankle fusion is in a relatively safe inter-nervous plane. Some adverse events were related directly to the implantation of the total ankle components such as malleolar fracture and bony changes (ingrowth, osteolysis or component loosening) and had no equivalent in the fusion arm. Indeed, malleolar osteotomy, per protocol, was done to perform a transmalleolar ankle fusion, and thus, was not considered an adverse event. The adverse events were based on the reports from each site; in retrospect the authors believe the threshold for identifying an adverse event may have been systematically slightly different between the two groups (and biased against the arthroplasty group) because of the comfort surgeons have with the fusion procedure and tolerance for minor intra or postoperative events.

In general the minor complications had little or no impact on ultimate outcome. Intra-operative peri-implant fractures healed during the period of immobilization required for the ankle replacement and were not associated with increased convalescence or morbidity. Most wound problems healed with local care and a short course of oral antibiotics. In the Pivotal Study, only one patient, a prednisone-dependent elderly female required revision of an ankle replacement to a fusion for wound difficulties.

In the Pivotal arthroplasty group, nine patients were reported to have nerve injury prior to discharge as determined by changes in sensation near the ankle or the foot. Of these nine patients, three patients had either partial or complete transections of nerves as part of the surgical approach to the ankle and two of the three had the nerve repaired intra-operatively. Additionally 23 other patients (32 total; 20%) had loss of some sensation in the foot, primarily in the region overlying the navicular tuberosity for at least one followup period following discharge. Loss of this sensation did not affect the patient's perceived outcome or satisfaction with the procedure. Sensory fibers emanating from the medial branch of the superficial peroneal nerve innervating this area were generally involved. There were no transections of the tibial, sural, or deep peroneal nerves in this subgroup. Although the rates of most adverse events markedly decreased between the initial Pivotal Study group and Continued Access arthroplasty groups, the rate of this occurrence and that of wound issues, approximately one in five cases, did not diminish, suggesting that this frequency of adverse events is likely inherent with use of the anterior approach to the ankle.

The current report on safety information is generally consistent with that reported previously, other than a remarkably low incidence of nonunion and subsequent revision in the arthrodesis arm of the trial. Perhaps the best data we currently have on this comes from a recent systematic review of total ankle arthroplasty and ankle arthrodesis that summarizes the extant information on both treatments. Haddad et al. reviewed 460 literature citations identifying only 49 studies considered of sufficient quality to include in their analysis.[19] Ten were ankle arthroplasty studies and 39

were arthrodesis studies. No head-to-head trials comparing these treatment methods were identified, and very limited prospective controlled data was available. From the pooled information on ankle arthrodesis in 1262 patients, the authors reported a mean nonunion rate of 10% (95% CI,7.4% to 12.1%). In the present comparative study the arthrodesis group had two non-unions among the 66 procedures, not the predicted seven. The remarkably low rate of non-unions may have been because of the strict inclusion/exclusion criteria, superior surgical skill, random chance, or lack of independent evaluation of each surgeons radiographs. Nevertheless, the low non-union rate we report had the effect of making attainment of safety non-inferiority for the Pivotal Study arthroplasty group challenging to achieve.

Overall, we report a higher rate of early major revision surgeries in the Pivotal Study arthroplasty group than the arthrodesis group. This report is consistent with that of Soohoo et al.[7] who analyzed data from all hospital discharges for patients undergoing ankle arthrodesis (4705) and ankle replacement (480) in California between 1995 and 2004. This same general finding is confirmed by the systematic literature review of Haddad et al.[19] In the present study, the rates of secondary major surgeries conducted within 24 months following surgery was higher for the Pivotal Study arthroplasty group than the arthrodesis group; however, the rates of secondary major surgeries were indistinguishable between the arthrodesis group and the Continued Access arthroplasty group in the first two years following surgery. The Continued Access group required half as many secondary minor and major surgeries as did the Pivotal Study arthroplasty group.

The implant was not modified between these two series. The decrease in secondary major procedures is likely due to increased surgeon experience and some modifications to the instruments and technique. The actual amount of surgeon experience required to get to the point where the learning curve flattens remains a question;[30,37,38,41] on average the surgeons performed 16 ankle replacements in the Pivotal Study arthroplasty group and 43 in the Continued Access group. The surgeon group also had variable experience with total ankle replacement prior to the initiation of the trial.

One clear change that came with experience related to the size of the talar implant. Initially surgeons tended to size the talar component large so it fit snugly into the mortise, theorizing that this would lead to better coverage and greater distribution of force across the talus. This led to a relatively high incidence of malleolar impingement, pain and need for a secondary procedure involving removal of bone from the medial or lateral gutters. These events and the removal of bone from the gutters were listed as safety failures although, in reality, the patients generally did well after these procedures with pain relief and improved ankle implant motion. With more experience and improved cutting and sizing guides, the fit of the talar component became more reproducible and functional, and the incidence of secondary procedures decreased.

The rate of major complications and revision surgeries for the STAR ankle replacement subjects in this entire study is substantially less than that reported by Spirt et al. for a series of Agility ankle replacements.[48] To our knowledge, Spirt et al.'s study[48] is the largest total ankle series reporting on 306 primary ankle arthroplasties followed for an average of less than 3 years. Of these, 85 patients (28%) underwent 127 reoperations (involving 168 procedures); whereas, at 24 months combining both the Pivotal and Continued Access arthroplasty patients, we report a rate of 11% re-operation on a per patient basis. Similar to the Spirt et al.[48] study, the most common procedure at the time of reoperation was débridement of heterotopic bone formation. In the current, prospective study we found a lower rate of amputations (1/593 vs. 8/306). This lower rate is similar to that reported by Soohoo et al.[47] and Haddad et al.[19] in their epidemiological survey and systematic reviews. The differences in rates of the current study compared with that reported by Spirt et al.[48] may be due to differences in study design (controlled prospective vs. retrospective), patient selection, followup period, concomitant procedures, surgical technique and implant design.

The radiographic analysis of STAR ankle replacements in the Pivotal Study demonstrated that neither initial periimplant radiolucencies nor minor initial implant settling were predictive of clinical failure. The lucencies were apparent around the flat tibial tray; whereas the settling was typically seen on the talar side. Seven of eight cases with initial periimplant lucencies eventually showed solid implant in-growth; five cases with minor settling (generally less than or equal to 5 mm) of the implant into bone stabilized within the first 12 months and, similarly, was not predictive of long-term clinical outcome at either 24 or 48 months. Seven other cases of settling continued to progress past 12 months and were considered radiographic and clinical failures.

By fault of the study design, the radiographic analysis was biased against the ankle replacement arm by non-equivalent intensity of analysis. Prior to study initiation, one center developed strict and clear criteria for taking and analyzing all the STAR ankle replacement radiographs. This protocol diminished radiographic interpretation problems arising from orientation malpositioning and ensured high quality office-based images for analysis. All images were digitized and analyzed by a single examiner for the pivotal study group. That examiner then trained a musculoskeletal radiologist to do the same analysis for the continued access study group, overlapping reading of approximately 100 radiographs to ensure consistency. We believe that the radiographic results reported herein are extremely accurate and reproducible.

A clear limitation of the study was related to not using a uniform and nonbiased approach to analyze the fusion radiographs. All fusion radiographs were interpreted by the surgeon of record. Status of fusion was not independently verified. This is a clear limitation of the study as delayed

unions, nonunions and malunions may have been underreported.

The STAR ankle incorporates a mobile bearing which is purported to allow motion with retained congruency. The reported disadvantages of a mobile bearing include dislocation, two sided wear and fracture. In this series of 415 STAR ankle replacements followed prospectively for 2 years with radiographic followup, we have identified four mobile bearing fractures, one case of wear requiring cystic lesion grafting and revision, and no mobile bearing component dislocations. Longer-term followup is needed to assess ultimate durability of the design.

In this prospective study of the STAR arthroplasty compared with a concurrent arthrodesis control and a second cohort of Continued Access arthroplasty subjects, we found superior overall patient success in the arthroplasty groups. Using a minimum net improvement of 40 points in the BP Ankle Score as a measure of efficacy at 24 months postsurgery, ankle replacement was superior to ankle fusion.

A weakness of the BP criteria is that it is not a validated instrument. At the time of the initiation of the study, there was no validated instrument widely available with data that could be used to estimate a clinically meaningful change in efficacy. It was chosen as a means to differentiate the efficacy of ankle arthroplasty versus fusion. It does give 15% credit for ankle motion. Thus a prosthesis that maintains or restores motion is favored by the scale over a fusion. Since motion of the ankle is important throughout stance phase, and loss of motion is associated with meaningful impairments, the authors considered the attribution of 15% credit in the BP scale to be appropriate

In the Pivotal Study, at 24 months following surgery, 58.5% of the STAR patients and only 14.9% of the fusion patients were deemed a success based on the criteria of a 40 point change in the BP scale. One should not conclude that this defines the true success of the surgery, as a high percentage of both the arthroplasty and fusion patients (greater than or equal to 85%) were indeed pleased and satisfied, and the removal of motion as a criteria of success diminishes any differences seen in the relative efficacy rates.

On an individual subscale basis, ankle arthroplasty was equal or superior to fusion in all areas of efficacy evaluated. Non-inferiority of ankle replacement safety was not met with the initial analysis. We think this was partially due to the relative paucity of non-unions in the control group and partially because the initial study radiographic safety criteria allowed a) inappropriate carrying forward of radiographic information and b) classified some cases as radiographic failures that have not borne out to be clinical failures. Post-hoc re-analysis suggests non-inferiority of arthroplasty safety compared with arthrodesis safety. Longer-term followup is required to better understand the durability and functional longevity of the STAR in this cohort.

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APPENDIX 1

BUECHEL-PAPPAS SCALE[1]

I. **PAIN**	(MAX. 40 POINTS)
None	40 points
Slight	35 points
Mild	30 points
Moderate	20 points
Severe	10 points
Totally Disabled	0 points
II. **FUNCTION**	(MAX. 40 POINTS)
LIMP	
None	8 points
Mild	6 points
Moderate	3 points
Severe	1 point
Unable to walk	0 points
STANDING	
No support for 3/4 hour	8 points
No support for 1/2 hour	6 points
No support for 1/4 hour	3 points
Unable to stand without support	0 points
WALKING	
Unlimited	8 points
6 blocks	6 points
2-3 blocks	4 points
Indoors only	2 points
Bed & chair	0 points
STAIRS	
Normally without banister	8 points
Normally with banister	6 points
External support and banister	3 points
Not able	0 points
SUPPORT	
None	8 points
Single cane for long walks	6 points
Single cane most of the time	4 points
1 crutch most of the time	3 points
2 canes most of the time	2 points
2 crutches/walker most of the time	0 points
III. **RANGE OF MOTION** (Clinical)	(MAX. 15 POINTS) (SPECIFY:____° TO___°)
Dorsiflexion 15°—Plantarflexion 45° or equal to unaffected contralateral ankle	15 points
Dorsiflexion 5°—Plantarflexion 30°	13 points
Combined motion 25° to 34°	11 points
Combined motion 15° to 24°	9 points
Combined motion 5° to 14°	5 points
Combined motion less than 5°	0 points
IV. **DEFORMITY**	(MAX. 5 POINTS) (CHECK ALL THAT APPLY)
Heel varus ? valgus ?	
If less than 6°	1 point
Equinus, dorsiflexes to neutral	1 point
Calcaneus, plantarflexes to 20°	1 point
Limb-length discrepancy less than 1.5 cm	1 point
Swelling, less than 1+ edema	1 point

APPENDIX 2

Radiographic measurement technique:

Joint space height:

a. AP/mortise view,
b. A line was fitted to the superior edge of the of the talar component.
c. Joint space height is defined as the perpendicular distance from this line to the tip of the medial malleolus is the joint space height.

AP position of the talus and height of the talus:

a. Lateral view
b. A circle was fitted to the superior surface of the talar component.
c. A line was dropped perpendicular to the floor through the center of this circle.
d. The perpendicular distance from this line to the anterior/superior aspect of the talus is the AP position of the talus
e. The height of this circle above the floor is the talus height.

Angle A:

a. Lateral view
b. Line fitted to the tibial midshaft and a line along the inferior edge of the tibial component
c. Angle A is the angle between these lines

Angle B:

a. Lateral view
b. Line connecting the posterior/inferior and anterior/superior aspects of the talus. A second line between the anterior and posterior limits of the talar component.
c. Angle B is the angle between these lines

Angle C:

a. AP/mortise view
b. Line fitted to the tibial midshaft and a line along the inferior edge of the tibial component
c. Angle C is the angle between these lines

APPENDIX 3

Sample Size Justification

Safety Endpoint

Definitions

Success (S.T.A.R. Ankle group): No major complication, device removal/revision, loosening, subsidence, migration, and plantigrade foot.

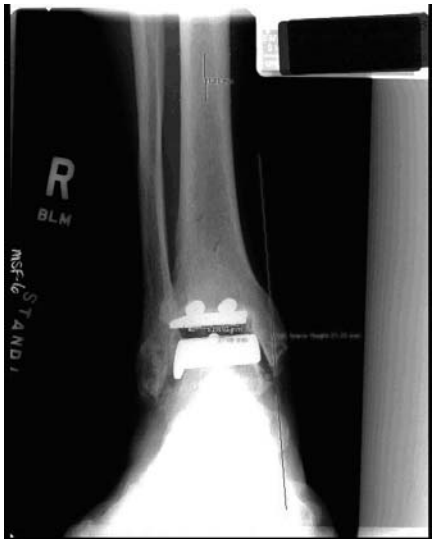

Fig. 1: AP radiograph measurement.

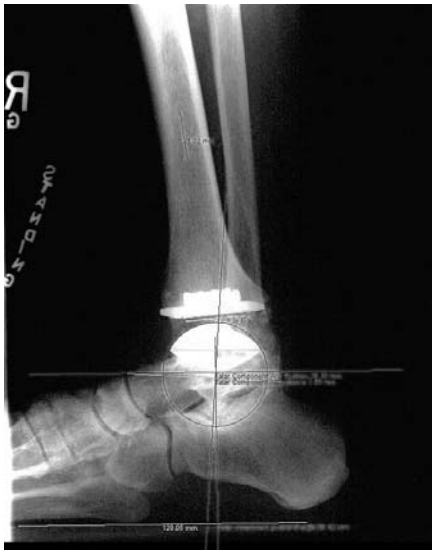

Fig. 2: Lateral radiograph measurement.

Success (Arthrodesis group): No major complication, non-union, delayed union, mal-union, revision, and plantigrade foot.

π_e: Proportion of successes in the Experimental treatment (STAR Ankle) group

π_c: Proportion of successes in the Control treatment (Ankle Arthrodesis) group

Hypotheses (method of Blackwelder[2]):

$$H_0 : \pi_c \geqslant \pi_e + \delta$$

$$H_1 : \pi_c < \pi_e + \delta$$

Type I error: the difference $\pi_c - \pi_e$ is less than δ when in fact the difference is greater than or equal to δ, *i.e.*, we choose the experimental treatment when the control treatment is actually substantially better.

Type II error: the difference is greater than or equal to δ when it is actually less than δ *i.e.*, we chose the control treatment when the experimental treatment is essentially just as good.

Assumptions and Calculations

$\alpha = 0.05$	(Probability of Type I error)
$\beta = 0.20$	(Probability of Type II error; power $= 1 - \beta$)
$\pi_c = \pi_e =$ 0.80	(Estimated success rate for control and treatment groups)
$\delta = 0.15$	(Difference that can be considered clinically insignificant: $\pi_c - \pi_e < \delta$)
$\lambda = 1.5$	(For 2:1 experimental:control ratio)

Sample size (when $\pi = \pi_c = \pi_e$)

$$N = \frac{\lambda(Z_{1-\alpha} + Z_{1-\beta})^2 \pi(1-\pi)}{\delta^2} = 67 \text{ Arthrodesis}$$

$\rightarrow$ 134 STAR ankle

Primary Efficacy Endpoint: Total Buechel-Pappas Scale score

Definitions

μ_e: Mean Total Buechel-Pappas Score in the Experimental treatment (STAR Ankle) group

μ_c: Mean Total Buechel-Pappas Score in the Control treatment (Ankle Arthrodesis) group

Hypotheses:

$$H_0 : \mu_e \geqslant \mu_c + \delta$$

$$H_1 : \mu_e < \mu_c + \delta$$

Type I error: the difference $\pi_e - \pi_c$ is less than δ when in fact the difference is greater than or equal to δ, *i.e.*, we choose the experimental treatment when the control treatment is actually substantially better.

Type II error: the difference is greater than or equal to δ when it is actually less than δ, *i.e.*, we chose the control treatment when the experimental treatment is essentially just as good.

Assumptions and Calculations

$\alpha = 0.05$	(Probability of Type I error, one sided)
$\beta = 0.20$	(Probability of Type II error; power $= 1 - \beta$)
$\sigma = 11.3$	(Population standard deviation, from New Jersey LCS paper[1])
$\delta = 10.0$	(Difference that can be considered clinically significant)
$\lambda = 1.5$	(For 2:1 experimental:control ratio)

Sample size

$$N = \frac{\lambda(Z_{1-\alpha} + Z_{1-\beta})^2 \sigma^2}{\delta^2} = 12 \text{ Arthrodesis}$$

$\rightarrow$ 24 STAR Ankle

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