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## Treatment of osteochondral lesions of the talus: a systematic review

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**Abstract** The aim of this study was to summarize all eligible studies to compare the effectiveness of treatment strategies for osteochondral defects (OCD) of the talus. Electronic databases from January 1966 to December 2006 were systematically screened. The proportion of the patient population treated successfully was noted, and percentages were calculated. For each treatment strategy, study size weighted success rates were calculated. Fifty-two studies described the results of 65 treatment groups of treatment strategies for OCD of the talus. One randomized clinical trial was identified. Seven studies described the results of non-operative treatment, 4 of excision, 13 of excision and curettage, 18 of excision, curettage and bone marrow stimulation (BMS), 4 of an autogenous bone graft, 2 of transmalleolar drilling (TMD), 9 of osteochondral transplantation (OATS), 4 of autologous chondrocyte implantation (ACI), 3 of retrograde drilling and 1 of fixation. OATS, BMS and ACI scored success rates of 87, 85 and 76%, respectively. Retrograde drilling and fixation scored

88 and 89%, respectively. Together with the newer techniques OATS and ACI, BMS was identified as an effective treatment strategy for OCD of the talus. Because of the relatively high cost of ACI and the knee morbidity seen in OATS, we conclude that BMS is the treatment of choice for primary osteochondral talar lesions. However, due to great diversity in the articles and variability in treatment results, no definitive conclusions can be drawn. Further sufficiently powered, randomized clinical trials with uniform methodology and validated outcome measures should be initiated to compare the outcome of surgical strategies for OCD of the talus.

**Keywords** Ankle · Osteochondral lesion · Defect · Talus · Systematic review · Arthroscopy

### Introduction

Symptomatic osteochondral ankle defects often require surgical treatment. An osteochondral ankle defect is a lesion of the talar cartilage and subchondral bone mostly caused by a single or multiple traumatic events, leading to partial or complete detachment of the fragment. The defects cause deep ankle pain associated with weightbearing. Impaired function, limited range of motion, stiffness, catching, locking and swelling may be present. These symptoms place the ability to walk, work and perform sports at risk.

The injury was classified by Berndt and Harty in 1959 [6]. Anatomic studies on cadaver limbs demonstrated the etiological mechanism of transchondral fractures of the lateral border of the talar dome. As the foot is inverted on the leg, the lateral border is compressed against the face of the fibula (stage I), while the collateral ligament remains intact. Further inversion ruptures the lateral ligament and

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begins avulsion of the chip (stage II), which may be completely detached but remain in place (stage III) or be displaced by inversion (stage IV). Berndt and Harty experimentally proved the traumatic etiology of the lesion; however, non-traumatic lesions also occur.

Treatment strategies for osteochondral defects (OCDs) of the ankle have substantially increased over the last decade. The widely published treatment strategies of symptomatic osteochondral lesions include the non-surgical treatment with rest or cast immobilization, and surgical excision of the lesion, excision and curettage, excision combined with curettage and drilling/microfracturing (i.e., bone marrow stimulation, BMS), placement of an autogenous (cancellous) bone graft, antegrade (transmalleolar) drilling (TMD), retrograde drilling, fixation and newer techniques like osteochondral transplantation (osteochondral autograft transfer system, OATS) and autologous chondrocyte implantation (ACI). The last two techniques focus at replacement and regeneration of hyaline cartilage, respectively.

The goal of these treatment strategies is to diminish symptoms like pain and swelling, and to improve function. Publications on the effectiveness of these treatment strategies vary. In most cases, several treatment options are viable, and the choice of treatment is based on the type and size of the defect and on preferences of the treating clinician.

The last systematic review concerning treatment strategies for OCDs of the talar dome was an update of a previous review [57] and included studies up to June 2000 [61]. However, since this date many studies concerning the newer techniques ACI [4, 16, 40, 63] and OATS have been published [1, 15, 17, 20, 28, 31, 47, 49, 50]. The aim of this study is to provide an up to date overview by pooling those studies dealing with treatment strategies for osteochondral ankle defects in order to summarize the effectiveness of these strategies.

## Patients and methods

Electronic databases MEDLINE, EMBASE, CENTRAL and DARE (January 1966–December 2006) were screened. As main key words ‘Therapy; Treat\*; Talus; Talar; Ankle; Cartilage\*; Osteochondritis Dissecans; Chondral; Osteochondral and Transchondral were used. The search strategy for MEDLINE was as follows: (therapy or treat\$) and (talar or talus or ankle) and (cartilag\$ or osteochondritis dissecans or talar or chondral or osteochondral or transchondral). No language limitations were imposed. The reference lists of all the articles selected were screened for additional articles.

All RCTs or quasi-experimental research that evaluated the effectiveness of treatment strategies for osteochondral

lesions of the talus were included. This included case series. Published studies describing the results of the following treatment strategies were included: non-operative treatment—rest, non-operative treatment—cast, excision of the fragment, excision and curettage, excision and curettage and drilling/microfracturing, placement of a cancellous bone graft, antegrade (transmalleolar) drilling, OATS, ACI, retrograde drilling and fixation of the lesion. Studies/patients were excluded if: a combination of diagnoses was evaluated, and results were not separately described for the osteochondral talar lesion group, follow-up was less than 6 months, therapy was inadequately described, patients were under 18 years old, less than 10 patients were included (excluding single case reports), the study was the lesser extensive of a double publication, there was no well-defined outcome and if there was a combination of therapies described, and results were not described per therapy. Two reviewers (MZ and DO) independently assessed the articles for inclusion. Forms specifically developed for and tailored to this review were used. Agreement was needed for inclusion. In case of disagreement, the opinion of a third independent investigator (CvD) was decisive. To prevent investigator bias, scoring of the manuscript was blinded to author and institute.

Successful treatment was defined as an excellent or good result at follow-up, defined by an accepted scoring system, like the AOFAS Ankle/Hindfoot scale [24], the Hannover Scoring System [54] and others (see Table 2). If the success rate was not defined by the author, the results were integrated into the widely accepted scoring system of Thompson and Loomer [56]. The proportion of the patient population treated successfully was noted, and percentages were calculated. For each treatment strategy, study size weighted success rates were calculated (for each treatment category: sum of the successfully treated patients divided by the total number of treated patients within that category).

The primary outcomes were the effects of treatment on symptoms, measured by scoring systems concerning the ankle (mainly the AOFAS Ankle/Hindfoot scale).

The Newcastle-Ottawa Scale (NOS) [62], adjusted for case series, was used for quality assessment of the included studies. It was originally developed as an instrument to provide an easy and convenient tool for quality assessment of nonrandomized studies, i.e., case–control and cohort studies, to be used in a systematic review. The Newcastle-Ottawa Scale uses a “star” rating system to judge quality based on three aspects of the study: selection of study groups, comparability of study groups and ascertainment of either the exposure or outcome of interest (dependent on assessment of case–control or cohort study, respectively). The maximum number of stars a study may receive in each of these three categories is 4, 1 and 3, respectively, for a

total of 8 possible stars. The validity of the scale has been previously established. In orthopedic literature, the vast majority of publications involve case series. We adjusted the NOS for case series to perform a quality assessment of the included case series. Studies were scored for study design, selection and assessment of outcome. The maximum numbers of stars a study could receive in the NOS adjusted for case series was 2, 1 and 2, respectively, for a total of 5 possible stars (Appendix 1).

## Results

### Description of studies

The search strategy identified over 2,000 articles. A total of 183 publications describing the results of treatment of talar osteochondral lesions could be identified. One randomized clinical trial was found [17]. Therefore, the conventional measures of summarizing estimates of effectiveness could not be used. We used pooling of the estimates of the outcome in individual studies.

Hundred and thirty-one studies were excluded due to one or more exclusion criteria, being: combination of diagnoses ( $n = 14$ ), inappropriate duration of follow-up ( $n = 14$ ), improper description of therapy ( $n = 8$ ), age under 18 years ( $n = 17$ ), case report ( $n = 33$ ), double publication ( $n = 17$ ), non-interpretable results ( $n = 37$ ), less than 10 patients ( $n = 37$ ) and a combination of therapies ( $n = 25$ ) (Table 1). This left 52 studies describing the results of 65 treatment groups. Three described the results of non-operative treatment—rest, 4 of non-operative treatment—cast, 4 of excision, 13 of excision and curettage, 18 of excision and curettage and BMS, 3 of retrograde drilling, 4 of ACI, 9 of OATS, 1 of fixation with bone pegs, 4 of cancellous bone grafting and 2 of antegrade (trans-malleolar) drilling.

**Table 1** Criteria that were used

Exclusion criteria	No.
Combination of diagnoses	14
Follow-up <6 months	14
Therapy inadequately described	8
<18 Years old	17
Single case report	33
Double publication	17
No well-defined outcome	37
<10 Patients	37
Combination of therapies	25
Total no. of excluded studies	202

### Population characteristics

The total number of included patients with osteochondral talar lesions in the 52 studies was 1361. The average age was 31 years [18–75], 63% were male and 37% female. The right ankle was involved in 57%, the left in 43%. Lesions were medial in 62%, lateral in 36%, central in 1% and medial and lateral in 1%. A history of ankle trauma was reported in 86% of cases. There was a primary defect in 84%. For about half of the patients, the Berndt and Harty stage was mentioned. In 13%, it considered a Berndt and Harty stage 1 lesion, in 22% a stage 2 lesion, in 40% a stage 3 lesion and in 25% a stage 4 lesion. The AOFAS Ankle/Hindfoot scale was most used [24] (Table 2).

### Treatment strategies

#### *Non-operative treatment: rest*

This may be rest and/or restriction of (sporting) activities with or without treatment of non-steroidal anti-inflammatory drugs (NSAIDs). The aim is to unload the damaged cartilage, so edema can resolve and necrosis is prevented. Another objective could be healing of a (partly) detached fragment to the surrounding bone. Three studies, 86 patients in total, described the results of rest for OCD [7, 45, 51]. Reasons to choose for non-operative treatment were not always clearly described. Two studies date from

**Table 2** Scoring systems used for treatment of talar osteochondral lesions in the included studies

Scoring system	No. of studies
AOFAS Ankle/Hindfoot scale	16
Scoring system developed by the authors	18
Hannover score	5
Patient satisfaction score	5
Criteria proposed by Berndt and Harty	5
Visual analog scale	3
Martin score	3
Alexander and Lichtman	3
Ogilvie Harris score	2
MODEMS	2
Karlsson scoring scale	2
Tegner score	1
Evaluation proposed by Loomer	1
Mazur score	1
Freiburg ankle score	1
SANE	1
According to Thompson and Loomer	1
McCullough score	1

Some studies used more than one scoring system

the past (1953 [45] and 1975 [7]), when surgical treatment of osteochondral talar lesions was not as common as it is today. In the majority of studies, the duration of symptoms prior to institution of non-operative treatment was either unreported or ranged from sub-acute to acute (<6 weeks) to chronic (>6 weeks). In the most recent study, patients were given the choice between operative and non-operative treatments, and the patient chose non-operative treatment. Conservative treatment consisted of weightbearing as tolerated [51]. In 39 of 86 patients (45%), conservative treatment reported to be successful (range 20–54%).

#### *Non-operative treatment: cast*

The aim is similar to the treatment option described previously, but then pursued by cast immobilization for at least 3 weeks up to 4 months. Four studies reported the results of this treatment [7, 10, 22, 41]. All date back at least two decades. The main reason to decide for cast immobilization was a Berndt and Harty stage II or III lesion. In 44 of the 83 patients (53%), the treatment was reported to be successful (range 29–69%).

#### *Excision*

The partially detached fragment is excised, and the defect itself is left untreated. The results were reported in four studies [12, 23, 37, 41]. In two studies, excision was performed for superficial cartilaginous lesions, with mainly intact underlying subchondral bone. Sometimes it involved a loose intra-articular fragment. In one study, the lesions involved bony necrosis underneath. In 32 of 59 patients, the result was reported to be successful (54%). Success rates varied from 30 to 88%.

#### *Excision and curettage*

After excision of the loose body, the surrounding necrotic subchondral tissue is curetted using either an open or arthroscopic technique. Most patients had a Berndt and Harty stage III or IV lesion, although also stage II lesions occurred. Thirteen studies, a total of 259 patients, reported the results of OCD treatment by excision and curettage [7, 10, 12, 17, 22, 23, 32, 33, 35, 38, 39, 42, 44]. In 199 of 259 patients, a successful result was reported (77%). The success rate varied from 56 to 94%.

#### *Excision, curettage and BMS*

Following excision and curettage (debridement), multiple connections with the subchondral bone are created. This can be accomplished by drilling or microfracturing. The objective is to partially destroy the calcified zone that is most often

present and to create multiple openings into the subchondral bone. Intra-osseous blood vessels are disrupted, and the release of growth factors leads to the formation of a fibrin clot. The formation of local new blood vessels is stimulated, bone marrow cells are introduced in the osteochondral defect, and fibro-cartilaginous tissue is formed. Patients often had a Berndt and Harty stage III or IV lesion, although stage I and II lesions occurred. Diameter of the lesions usually did not exceed 1.5 cm. A total of 18 studies, including 388 patients, described the results of BMS [2, 3, 5, 8, 11, 13, 14, 17–19, 21, 34, 36, 37, 48, 52, 55, 60]. In 329 of 386 patients, treatment was reported to be successful (85%). The success rate varied from 46 to 100%.

#### *Excision, curettage and autogenous bone graft*

In this technique, the defect that remains after excision, and curettage is filled with autogenous cancellous bone. The aim is to restore the weightbearing properties of the talus. Indications for treatment were large, often medial lesions, exceeding 1.5 cm in diameter. Four publications reported the results of this technique for 74 patients [9, 13, 25, 27]. In 45 of 74 patients, the result was successful. Success rates varied from 41 to 93%.

#### *Antegrade (transmalleolar) drilling*

In case an osteochondral lesion is hard to reach because of its location on the talar dome, the defect can be drilled through the malleolus. A K-wire is inserted about 3 cm proximal to the tip of the medial malleolus and directed across the medial malleolus into the lesion through the intact cartilage. Two publications described the results of this technique for 41 patients [26, 44]. In 26 patients, the result was reported to be successful (63%, range 32–100%).

#### *Osteochondral transplantation/OATS*

Osteochondral autografts have been introduced as an alternative to allografts for the treatment of OCDs. Two related procedures have been developed: mosaicplasty and OATS. Both are reconstructive bone grafting techniques that use one or more cylindrical osteochondral grafts from the less weightbearing periphery of the ipsilateral knee and transplant them into the prepared defect site on the talus. Its goal is to reproduce the mechanical, structural and biochemical properties of the original hyaline articular cartilage which has become damaged. It is carried out either by an open approach or by an arthroscopic procedure. Indications involve large, often medial lesions, sometimes with a cyst underneath. In some cases, it involves secondary treatment, after failed primary (surgical) treatment. Nine publications described the results of 243 patients treated by osteochondral

transplantation [1, 15, 17, 20, 28, 31, 47, 49, 50]. Good/excellent results were obtained in 212 patients (87%). Success rates varied from 74 to 100%. Morbidity of the donor knee joint was seen in 12% of patients (0–37%). Three studies did not discuss the possibility of post-operative knee pain [20, 28, 47].

#### *Autologous chondrocyte implantation/ACI*

Autologous chondrocyte implantation attempts to regenerate tissue with a high percentage of hyaline-like cartilage. By means of an arthroscopic approach, a region of healthy articular cartilage is identified, and a biopsy is taken. The tissue is minced and enzymatically digested. Chondrocytes are separated by filtration, and the isolated chondrocytes are cultivated in culture medium for 11–21 days. An arthrotomy is performed, and the chondral lesion is excised up to the healthy surrounding cartilage. A periosteal flap is removed from the tibia and is sutured to the surrounding rim of normal cartilage. The cultured chondrocytes are then injected beneath the periosteal flap. It is done for lesions larger than 1 cm<sup>2</sup>, in the absence of generalized osteoarthritic changes. Four studies, describing 59 patients, were included [4, 16, 40, 63]. In 45 of 59 patients (76%), a successful result was reported. The success rate varied from 70 to 92%.

#### *Retrograde drilling*

Retrograde drilling is done for primary OCDs when there is more or less intact cartilage with a large subchondral cyst, or when the defect is hard to reach via the usual

anterolateral and anteromedial portals. For medial lesions, arthroscopic drilling can take place through the sinus tarsi. For lateral lesions the cyst is approached from anteromedial. The aim is to induce subchondral bone revascularization and subsequently to stimulate the formation of new bone. A cancellous graft may be placed to fill the gap. Three studies, comprising 42 patients, were included [26, 46, 53]. It mainly involved medial lesions. Size of the lesions was not described. Post-operatively immediate range-of-motion exercises were commenced in all studies. Partial weightbearing was started 2, 4 or 6 weeks post-operatively [26, 46, 53]. In 37 of 42 patients, the treatment was reported to be successful (88%, range 81–100%).

#### *Fixation*

In case of a large loose fragment, one can choose to secure it to the underlying bone using either a screw, pin, rod or fibrin glue. One publication, for a total of 27 patients, met our inclusion criteria [29]. In this study, stage II–IV lesions were elevated, the bed was curetted and drilled, and after alignment of the fragment it was reattached with at least two bone pegs from the distal tibia. Results were reported to be successful in 24 patients (89%).

Results are summarized in Table 3.

#### Quality assessment of included studies

On ‘study design’, together 52 studies scored a total of 28 stars, out of a possible 104. Seven studies were prospective in design; however, most case series were retrospectively

**Table 3** Results per treatment strategy

Treatment strategy	No. of studies	No. of patients	No. of patients good/excellent result	Study weighted success rate (%)	Range (%)
Non-operative, rest	3	86	39	45	20–54
Non-operative, cast	4	83	44	53	29–69
Excision	4	59	32	54	30–88
Excision and curettage	13	259	199	77	56–94
Excision, curettage and BMS	18	388	329	85	46–100
Autogenous bone graft	4	74	45	61	41–93
TMD	2	41	26	63	32–100
OATS	9	243	212	87	74–100
ACI	4	59	45	76	70–92
Retrograde drilling	3	42	37	88	81–100
Fixation, bone pegs	1	27	24	89	–

Described are the number of included studies per treatment strategy as mentioned in the first column, the cumulative number of patients per treatment strategy, the number of patients with a good or excellent result at follow-up, the success percentage per treatment strategy and finally the range of the success percentages

*BMS* bone marrow stimulation, *ACI* autologous chondrocyte implantation, *OATS* osteochondral autograft transfer system, *TMD* transsalleolar drilling

executed [36], and in 9 studies, the pro- or retrospective nature of the study was not described. Twenty-one studies accounted for the protocol they had followed, but the majority of studies did not mention a protocol, or did not describe it properly. On ‘selection,’ 48 out of 52 possible stars were scored. Nearly all studies reported on a representative patient group. On ‘outcome’ 34 out of 104 stars were scored. In none of the studies, blind assessment was described (often it was not clear whether patients were scored by someone else than the author), and loss to follow up exceeded 5% in many cases.

## Discussion

The most important finding of the present study was that bone marrow stimulation (BMS) was identified as the best treatment option.

The review summarizes 65 study groups in 52 studies that describe treatment strategies for osteochondral talar lesions. There was a great diversity in trials concerning patient characteristics, staging of the defect, duration of follow-up and outcome measures. A relatively large number of studies were dedicated to treatment by excision and curettage, excision and curettage and BMS, and OATS. The number of patients in other categories, mainly retrograde drilling, fixation and transmalleolar drilling (TMD), was too limited for a reliable interpretation of the results. Therefore, no definitive conclusions can be drawn. Recommendations concerning these techniques must be judged in this light. Retrograde drilling is usually reserved for large OCDs with intact overlying cartilage, as confirmed by arthroscopy. It is the treatment of choice when there is a large subchondral cyst with overlying healthy cartilage. However, sizes of the lesions were not described in any of the studies concerning

retrograde drilling [26, 46, 53]. Fixation is indicated for lesions in which a large fragment can be reattached. It is applied especially in (sub)acute cases and in adolescents and children. Transmalleolar drilling is performed when a defect is hard to reach because of its location on the talar surface. A disadvantage is that healthy tibial cartilage is damaged. The reported results do not support the use of this technique [26, 44]. Besides, most talar lesions can be reached by means of the standard anterior or posterior arthroscopic approach, using intermittent distraction and a 90° microfracture probe [58, 59, 64].

The results of non-operative treatment were low compared to operative treatment. In spite of this, non-operative treatment should always be the first treatment to be considered.

Today, most publications on treatment of osteochondral lesions of the talus involve arthroscopic excision, curettage and bone marrow stimulation, ACI and OATS. They scored success percentages of 85, 76 and 87, respectively. ACI is a relatively expensive technique, and OATS gives morbidity from knee complaints in a relevant number of patients—up to 36% in literature [1, 15, 30, 43]. Therefore, we recommend arthroscopic excision, curettage and BMS to be the first treatment of choice for primary osteochondral talar lesions. It is relatively inexpensive, there is low morbidity, a quick recovery and a high success rate.

The results of this review differ slightly from the results described in the review of Verhagen et al. [61]. Results of both reviews are listed in Table 4. The success percentage for BMS has changed very little. Verhagen included 21 studies and 227 patients, and this review included 18 studies and 388 patients. The success rate went from 86 to 85%. For OATS, the success rate changed from 94 to 87%. Verhagen found one study with 36 patients treated with this technique. We identified nine eligible studies comprising 243 patients.

**Table 4** Success percentages (patients with a good/excellent result at follow-up after treatment of an osteochondral talar lesion) of a previous review by Verhagen et al. [61] compared to the current review

Treatment strategy	Verhagen et al. studies published up to 2000 (%)	Current review, studies published up to 2006 (%)
Non-operative treatment—rest	45	45
Non-operative treatment—cast	–	53
Excision	38	54
Excision and curettage	76	77
Excision, curettage and BMS	86	85
Autogenous bone graft	85	61
TMD	–	63
OATS	94	87
ACI	–	76
Retrograde drilling	81	88
Fixation	73	89
Total		76

In the previous review, the ACI technique was not included. We now identified four studies, comprising 59 patients, describing the results of ACI, leading to a success percentage of 76%. Our exclusion criteria were stricter than those of the previous review. Considering the number of patients, Verhagen et al. excluded single case reports, but included series of two patients and more. To be included in our review, each study group had to involve 10 patients or more. This excluded the ‘extended case reports’ and only allowed true case series to be evaluated. Our initial goal was to only include study groups of 20 patients or more. This protocol, however, excluded too many studies, and we stretched our criteria to 10 patients. In comparison with Tol [57], this eliminated 13 studies (and 18 treatment groups) and in comparison with Verhagen [61] it is 30 studies.

For the quality of the review, we would have preferred to include only the highest level of evidence, which are randomized clinical trials. However, only one RCT was identified, describing the results of chondroplasty (excision and curettage), microfracturing and osteochondral transplantation [17]. Looking at the set-up and inclusion of this study one, can debate whether this study was a truly randomized trial, as is also stated by the authors of the article. We identified no case control studies.

Assessment of quality by the adjusted NOS showed that studies scored low on study design. Studies scored moderately concerning ‘outcome’, since no study described whether blind assessment was part of the protocol, and in many studies there was a loss to follow up exceeding 5%. The NOS adjusted for case series, as used in this study, has not been validated. However, scoring low on the items described earlier leads to a higher chance of introducing bias.

The clinical relevance of the present study is the identification of the most effective treatment options for primary osteochondral lesions of the talus, which can serve as a guideline for treatment in clinical practice.

## Conclusion

Based on the current best available evidence, at present, treatment by means of debridement and bone marrow stimulation is the most effective treatment strategy for symptomatic osteochondral lesions of the talus. To draw definitive conclusions, sufficiently powered, randomized clinical trials with uniform methodology and validated outcome measures should be initiated.

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## Appendix 1: Newcastle: Ottawa quality assessment scale

Adjusted for case series

### Study design

1. Type of study
  - a. Prospective\*
  - b. Retrospective
  - c. Other
  - d. Not described
2. Set-up
  - a. According to protocol\*
  - b. Without protocol
  - c. No protocol described

### Selection

3. Representativeness of included patients
  - a. Truly representative of the average talar OCD patient in the community\*
  - b. Somewhat representative of the average talar OCD patient in the community\*
  - c. Selected group of patients by surgeon
  - d. No description of the derivation of the patient group

### Outcome

4. Assessment of outcome
  - a. Independent blind assessment\*
  - b. Record linkage\*
  - c. Self-report
  - d. No description
5. Adequacy of follow-up of series
  - a. Complete follow-up—all subjects accounted for\*
  - b. Subjects lost to follow-up unlikely to introduce bias—small number lost (<5%)\*
  - c. Follow-up rate < 95% and no description of those lost
  - d. No statement



Number of assigned stars

Study design	Selection	Outcome
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Every included study was separately assessed for quality using an adjusted version of the Newcastle Ottawa Scale, as described earlier. It was performed by scoring each study for study design (0–2 stars), selection of patients (0–1 star) and outcome (0–2 stars). The designs that earned a star are marked with a \*. For each study, the total number of stars was noted in the box given

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