Comparison of artificial graft versus autograft in anterior cruciate ligament reconstruction: a meta-analysis

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Abstract

Background: Critically evaluation and summarization for the outcomes between autografts and artificial grafts using in anterior cruciate ligament (ACL) reconstruction have not been performed currently. The purpose of this study is to compare the clinical outcomes between artificial ligaments and autografts at a short- to mid-term follow-up.

Methods: A computerized search of the databases was conducted including Medline, Embase, and the Cochrane library. Only prospective or retrospective comparative studies with a minimum 2-year follow-up and a minimum sample size of 15 for each group were considered for inclusion. Two independent reviewers performed data extraction and methodological quality assessment. A Mantel-Haenszel analysis was used for pooling of results. Sensitivity analysis was performed in order to maintain the stability of results.

Results: Seven studies were included in this study. The total sample size was 403 (autograft group: 206 patients; synthetic graft group: 197 patients). Four studies were randomized controlled trials. Two studies were retrospective comparative studies and one study was non-randomized prospective comparative study. In terms of instrumented laxity, patient-oriented outcomes and complications, no significant difference was occurred between new artificial ligaments and autografts. But the results of IKDC grades and instrumented laxity were worsen in early artificial ligaments compared to autografts.

Conclusions: The outcomes of new generation of artificial ligaments are similar to autografts at a short- to mid-term follow-up. However, the early artificial ligaments are not suggested for ACL reconstruction compared to autografts.

Keywords: Artificial ligament, Autograft, Anterior cruciate ligament, Reconstruction
synovitis have been reported as major disadvantages of synthetic grafts [6–8].
A few conventional narrative reviews have addressed related issues about the graft selection for ACL reconstruction [9–12]. Firm conclusions regarding the clinical outcomes with autografts or synthetic grafts cannot be drawn from those narrative reviews due to some inherent bias. Moreover, there have already been systematic reviews and meta-analysis which compared the clinical outcomes between allografts and autografts using in ACL reconstruction [13–16]. Critically evaluation and summarization for the outcomes between autografts and synthetic grafts using in ACL reconstruction have not been performed currently.

Using the best available evidence, the purpose of this research is to compare synthetic grafts with autografts in ACL reconstruction by evaluation the clinical outcomes including the results of instrumented laxity, patient-oriented outcomes, complications and graft failures.

Methods

Searching strategy

This research was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [17]. Two researchers searched the international databases independently up to December 30th, 2016, including Medline, Embase, and the Cochrane library. OpenGrey, the World Health Organization International Clinical Trials Registry Platform, the International Standard Randomised Controlled Trial Number (ISRCTN) registry, and Current Controlled Trials were searched to review the trial registry and grey literature. There was no restriction to years of publication and languages.

Eligibility criteria

Eligibility criteria were as follows: 1) a clinical study with a prospective or retrospective comparative design (Level of Evidence I, II, or III) [18]; 2) patients with no limitation of race and sex undergoing primary ACL reconstruction; 3) a study of ACL reconstruction comparing autografts with synthetic grafts and no restriction for types; 4) the outcomes being evaluated including physical examinations, complications, or patient-oriented outcomes etc.; 5) at least 2 years follow-ups; 6) at least 15 sample size for each group [15]. Knee laxity assessments included the arthrometer test and physical examinations (Lachman test and pivot-shift test). The details were shown in Table 1.

Any researches that failed to meet the inclusion criteria were excluded. In addition, a study was excluded if data from the same patients were reported in another study that had longer follow-up.

Data extraction and quality assessment

Two reviewers independently performed data extraction and quality assessment. In case of discrepancies, any controversy was resolved by further discussion with the corresponding author. The extraction included the following: (1) the characteristics of included researches (author, publication date, study design, participants’ demography, sample size, and duration of follow-up); (2) the details of methodology (implant type and drilling technique); (3) the details of outcomes. In our research, Newcastle-Ottawa Scale (NOS) was used to assess quality for cohort study while Jadad scale was used to assess quality for randomized controlled trial (RCT) [19, 20].

Statistical analysis

The meta-analysis was conducted using RevMan Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Using the same format, two reviewers independently collected data and crosschecked the results. Disagreements were discussed with the corresponding author and reached consensus in order to ensure accuracy.

Odds ratio (OR) with 95% confidence interval (CI) was calculated for dichotomous while mean difference (MD) with corresponding 95% CI was calculated for continuous outcomes. Statistical heterogeneity was assessed by calculating the heterogeneity index $I^2$. When heterogeneity was significant ($I^2 > 50$%), a Mantel-Haenszel analysis utilizing a random-effects model was used; otherwise a fixed-effects model was used when heterogeneity was considered as low ($I^2 \leq 50$). Funnel plots were used to test publication bias and a relatively symmetric funnel plot indicated inexistence of obvious publication bias. Sensitivity analysis was performed in order to maintain the stability of results.

Results

Article selection results

Three hundred and six relevant articles were initially selected according to the search strategy (Fig. 1). There were 161 articles left after checking for duplicates by using the literature management software Endnote X7. One hundred and forty-five articles were removed by screening the title and abstract. After reviewing the full text, 9 articles were excluded through assessment for eligibility. Eventually, 7 articles were included in qualitative and quantitative synthesis [21–27].

Characteristics of selected articles

All eligible studies were written in English from 1993 to 2013 (Table 2). Two studies were conducted in a North American country, and three studies were conducted in a European country. The other two studies were conducted in China. Among these studies, the synthetic
The graft used to compare with autograft included the Ligament Advanced Reinforcement System (LARS) artificial ligament (3 studies), the Leeds-Keio (LK) artificial ligament (2 studies), the Ligament Augmentation Device (LAD) (1 study) and the polyglycolic acid Dacron (PGA-Dacron) graft (1 study). The autograft used for comparison was BPTB (6 studies) and hamstring tendon (1 study). The rate of follow-up was ≥90% and the follow-up periods were ≥24 months in all included studies. The total sample size was 403 patients (autograft group: 206 patients; synthetic graft group: 197 patients). The release source and release date of each artificial ligament were shown in Table 3.

Table 1 Knee laxity assessment of included studies

| Included studies | Arthrometer testing | Flexion angle/° | Load level/N | Physical examination | Time from surgery to test/month |
|------------------|---------------------|-----------------|--------------|----------------------|---------------------------------|
| Engstrom 1993    | Knee Laxity Tester; Stryker | 20 | NR | x | 12-50 |
| Ghalayini 2010   | Stryker laxometer; Stryker | NR | NR | √ | 60 |
| Grøntvedt 1995   | KT-1000 arthrometer; MEDmetric | 20 | 89 | √ | 24 |
| Liu 2010         | KT-1000 arthrometer; MEDmetric | 30 | 134 | x | 48-52 |
| Nau 2002         | Instrumented Laxity Tester; Telos | 20 | 250 | x | 24 |
| Pan 2013         | KT-1000 arthrometer; MEDmetric | 30 | 134 | x | 48-54 |
| Pritchett 2009   | KT-1000 arthrometer; MEDmetric | 30 | 134 | x | 84-228 |

NR not reported.

Fig. 1 Flowchart of article selection process
| Study       | Journal                  | Implant       | Followups (months) | Autograft | No. of patients | Age   | Gender (Male/Female) | Synthetic graft | No. of patients | Age   | Gender (Male/Female) | Outcome                                                                 |
|-------------|--------------------------|---------------|-------------------|-----------|----------------|-------|---------------------|----------------|----------------|-------|---------------------|--------------------------------------------------------------------------|
| Pan 2013    | Eur J Orthop Surg Traumatol | BPTB          | LARS              | 50 (48–54)| 30             | 33.9  | 19/11               | 32             | 35.9          | 25/7          | Anterior laxity; IKDC score; Lysholm score; Tegner score                |
| Ghalayini 2010 | Knee                   | BPTB          | LK                | 60        | 26             | 309   | 19/7                | 24             | 31.7          | 21/3          | Anterior laxity; IKDC score; Lysholm score; Tegner score; one-hop test |
| Liu 2010    | Int Orthop               | HT            | LARS              | 49 (48–52)| 32             | 32    | 24/8                | 28             | 36            | 21/7          | Anterior laxity; IKDC score; Lysholm score; Tegner score                |
| Pritchett 2009 | J Knee Surg              | BPTB          | PGADacron         | 138 (84–228)| 35        | 25    | 24/11               | 35             | 26            | 23/12         | Anterior laxity; IKDC score; Lysholm score; KOOS                        |
| Nau 2002    | J Bone Joint Surg Br     | BPTB          | LARS              | 24        | 27             | 309   | 15/12               | 26             | 31.0          | 21/5          | Anterior laxity; IKDC score; Tegner score; KOOS                        |
| Grøntvedt 1995 | Scand J Med Sci Sports | BPTB          | LAD               | 24        | 26             | NR    | NR                  | 22             | NR            | NR            | Anterior laxity; Lysholm score; Tegner score; Isokinetic strength       |
| Endstrom 1993 | Clin Orthop Relat Res   | BPTB          | LK                | 28        | 30             | 23.8  | 14/16               | 30             | 23.4          | 21/9          | Anterior laxity; IKDC score; Lysholm score; Tegner score; Muscle performance |

BPTB bone-patellar tendon-bone, LARS ligament advanced reinforcement system, LK Leeds Keo synthetic graft, HT hamstring tendon, LAD ligament augmentation device, PGA-Dacron polyglycolic acid-Dacron, IKDC International Knee Documentation Committee, KOOS Knee Injury and Osteoarthritis Outcome Score, NR not reported

*The mean age and the gender distribution were not described separately in this study. The mean age of the patients was 25 years (range 15–42). There were 18 men and 30 women altogether including in this research.
The synthetic grafts were divided into two groups (Group 1: early generation; Group 2: new generation) for analysis. In this study, the early generation of the artificial ligaments contained the LK artificial ligament and the LAD, while the new generation included the LARS artificial ligament and the PGA-Dacron graft [2, 26]. Among all included articles, 4 articles were related to the new generation and 3 articles were related to the old generation (Table 2).

Quality of selected articles
Assessment of the methodological quality revealed that there were four RCTs (Level I). Two studies were retrospective comparative studies (Level III) and one study was non-randomized prospective comparative study (Level II). Among these four RCTs, only one article was of high quality with scores ≥4 while the other three articles were of low quality with scores ≤3 according to Jadad scale (Table 4). Assessed by NOS scale, two retrospective studies and one prospective study were of high quality. All demographic data were compared between two groups and showed no significant difference in eligible studies.

Meta-analysis
Instrumented laxity
All included studies tested instrumented laxity. The study of Nau et al. was excluded for providing quantitative data other than grade data of instrumented laxity (> 5 mm or ≤5 mm), which could not be compared with other studies [22]. No heterogeneity was found among the studies. Using the fixed-effects model in analysis, the early generation of synthetic grafts had a significant difference in knee laxity compared with autografts and the synthetic graft had a poorer result (OR = 11.44; 95% CI: 2.46, 53.16; \( p = 0.98; I^2 = 0\% \); Fig. 2a). Conversely, the new generation of synthetic graft showed no significant difference in knee laxity compared with autografts (OR = 0.63; 95% CI: 0.21, 1.93; \( p = 0.44; I^2 = 0\% \); Fig. 2b).

Physical examinations
Two studies assessed the anterior stability by Lachman test and two studies evaluated the rotational stability through pivot-shift test (Table 1). All included studies were related to the early artificial ligaments (LK artificial ligament and LAD). The Lachman test showed a poorer result in the early synthetic grafts than in the autografts (OR = 0.02, 95% CI: 0.00, 0.41), indicating a worse anterior stability. The result of pivot-shift test was poor in early synthetic grafts (OR = 0.03, 95% CI: 0.01, 0.16), documenting a worse rotational stability comparing to autografts.

International knee documentation committee (IKDC) grades
Six studies reported postoperative IKDC grades but the study of Nau et al. was excluded for providing the different type of categorical data comparing to other included studies [22]. No heterogeneity was found and a fixed-effects model was used to analysis (Fig. 3). There were 51 patients in the early synthetic graft group and 50 patients in the autograft group. The early synthetic grafts (LK, LAD) had worsen IKDC grades (OR = 3.41; 95% CI: 1.30, 8.89; \( p = 0.57; I^2 = 0\% \); Fig. 3a). Altogether 95 cases in the new synthetic graft group and 97 cases in the autograft group were reported. The new synthetic grafts (LARS) had no difference in IKDC grades compared to autografts (OR = 0.72; 95% CI: 0.35, 1.48; \( p = 0.90; I^2 = 0\% \)).

Table 3 Details of each artificial ligament in included study

| Included studies | Synthetic product name | Release source | Release date |
|------------------|------------------------|----------------|--------------|
| Engstrom 1993    | Leeds-Keio graft       | Neoligaments, Leeds, UK | 1980         |
| Ghalayini 2010   | Leeds-Keio graft       | Xiros plc formerly Neoligaments Ltd., Leeds, UK | 1980         |
| Grøntvedt 1995   | LAD                    | 3 M Company, St. Paul, Minnesota, USA | 1980         |
| Liu 2010         | LARS artificial ligament | Surgical Implants and Devices, Arc-sur-Tille, France | 1985         |
| Nau 2002         | LARS artificial ligament | Surgical Implants and Devices, Arc-sur-Tille, France | 1985         |
| Pan 2013         | LARS artificial ligament | Surgical Implants and Devices, Arc-sur-Tille, France | 1985         |
| Pritchett 2009   | PGA-Dacron graft       | Surgitex, Southfield, Mich | NR           |

LAD ligament augmentation device, LARS ligament advanced reinforcement system, PGA-Dacron polyglycolic acid-Dacron, NR not reported

Table 4 Quality assessment of included studies

| Study       | Level of evidence | Type               | NOS | Jadad scale |
|-------------|-------------------|--------------------|-----|-------------|
| Pan 2013    | III               | Retrospective study| 7   | 5           |
| Ghalayini 2010 | I               | RCT                | 5   |             |
| Liu 2010    | III               | Retrospective study| 7   | 3           |
| Pritchett 2009 | II              | Prospective study  | 7   |             |
| Nau 2002    | I                 | RCT                | 3   |             |
| Grøntvedt 1995 | I               | RCT                | 1   |             |
| Endstrom 1993 | I                | RCT                | 1   |             |

NOS Newcastle-Ottawa Scale, RCT randomized controlled trial
**Lysholm scores**

Six eligible studies tested postoperative Lysholm scores but the results of two studies could not be analyzed in meta-analysis. One was excluded due to lack of standard deviation and the other was due to suppling Lysholm scores as grade data other than quantitative data [21, 24]. Three studies were in Group 2 while only one study was in Group 1. There were altogether 95 cases in Group 2 and 97 cases in the autograft group. Heterogeneity was not found among these three studies and a fixed-effects model was used ($p = 0.88$; $I^2 = 0\%$), showing no significant difference in the Lysholm scores between two groups (OR = 1.80; 95% CI: -0.52, 4.13).

**Tegner scores**

Six studies reported Tegner scores but only 3 studies applied mean scores and standard deviations [23, 25, 27]. The rest three studies documented there was no significant difference between two groups in their longest follow-up time. Two studies were related to the new generation of the synthetic grafts and one study were focused on the old generation. Heterogeneity was not significant and a fixed-effects model was used, no significant difference occurred in new synthetic grafts and autografts (OR = 0.40; 95% CI: -0.09, 0.89).

**Complications**

Six studies evaluated complications of ACL reconstruction. The study conducted by Endstrom et al. did not report the complications after ACL reconstruction and was excluded for analysis. No heterogeneity was found and a fixed-effects model was used ($I^2 = 0\%$; Fig. 4). Altogether 44 patients were included in the early synthetic graft group and 50 patients were included in

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### Lysholm scores

| Study or Subgroup | Synthetic grafts | Autografts | Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|-------------------|-----------------|------------|-------|--------|------------------------------|
| Gronvhedt 1995    | 7               | 22         | 29    | 46.2%  | 11.67 [1.30, 104.34]         |
| Ghalayini 2010    | 0               | 22         | 22    |        | Not estimable                |
| Endstrom 1993     | 9               | 29         | 38    | 53.8%  | 11.25 [1.31, 96.39]          |
| **Total (95% CI)** | **73**          | **76**     | **16**| **100.0%** | **11.44 [2.46, 53.16]** |

**Heterogeneity:** Chi$^2 = 0.00$, df = 1 ($p = 0.98$); $I^2 = 0\%$

**Test for overall effect:** $Z = 3.11$ ($p = 0.002$)

### Tegner scores

| Study or Subgroup | Synthetic grafts | Autografts | Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|-------------------|-----------------|------------|-------|--------|------------------------------|
| Liu 2010          | 0               | 28         | 28    | 40.6%  | 0.15 [0.01, 2.99]            |
| Pan 2013          | 3               | 32         | 35    | 23.6%  | 1.45 [0.22, 9.33]            |
| Prichett 2009     | 2               | 35         | 37    | 35.7%  | 0.65 [0.10, 4.13]            |
| **Total (95% CI)** | **95**          | **97**     | **5** | **100.0%** | **0.63 [0.21, 1.93]** |

**Heterogeneity:** Chi$^2 = 1.66$, df = 2 ($p = 0.44$); $I^2 = 0\%$

**Test for overall effect:** $Z = 0.80$ ($p = 0.42$)

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**Complications**

The study conducted by Endstrom et al. did not report the complications after ACL reconstruction and was excluded for analysis. No heterogeneity was found and a fixed-effects model was used ($I^2 = 0\%$; Fig. 4). Altogether 44 patients were included in the early synthetic graft group and 50 patients were included in

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**Fig. 2 Forest plot of the instrumented laxity. a the early generation of synthetic grafts; b the new generation of synthetic grafts**

**Fig. 3 Forest plot of the IKDC grades. a the early generation of synthetic grafts; b the new generation of synthetic grafts**
the compared group. No significant difference was found in the rate of complications between two groups (OR = 0.50; 95% CI: 0.16, 1.49; Fig. 4a). Similarly, no significant difference occurred in the new synthetic grafts and autografts (OR = 0.75; 95% CI: 0.14, 3.89; Fig. 4b).

Sensitivity analysis indicated that the study with regard to four-strand HT graft had no obvious deviation compared to other studies concerning about BPTB in evaluation of knee laxity, patient-oriented outcomes and the rate of complications.

**Publication bias**

Funnel plots of instrumented laxity and complications were used to evaluate the publication bias, showing the lack of obvious bias among the eligible studies related to new synthetic grafts according to a relative symmetric funnel plot (Figs. 5 and 6).

**Discussion**

The key findings of present meta-analysis indicated that, in general, the patient-oriented outcomes and the rate of complications of ACL reconstruction with synthetic grafts were not significantly different from those with autograft, especially for new generation synthetic grafts (LARS and PGA-Dacron). However, with regard to knee laxity, ACL reconstruction with early artificial grafts had obviously poorer knee laxity from those with autografts (95% CI: 1.03, 4.72) while new artificial grafts showed no significant difference with autografts (95% CI: 0.21, 1.93).
The LK artificial ligament was a polyester mesh-like structure intended as a scaffold for soft tissue ingrowth [28]. The LAD, a band-like braid of polypropylene, was designed to protect the autogenous graft from excessive stresses [29]. Murray et al. reported that 28% of the group were known to have ruptured the LK ligament and 56% had increased laxity compared to the opposite normal knee at a 10–16 year follow-up [30]. A study conducted since 1983, included 856 patients accepted ACL reconstruction with LAD, showed 63 cases of complications and 73 cases of re-surgery [31]. Long-term follow-up results documented both the LK artificial ligament and the LAD were not suitable as an ACL substitute [30–32]. Moreover, the LAD caused effusions and reactive synovitis in the knee for provoking inflammatory reactions, and was found to delay maturation of autogenous graft [33]. The knee laxity and the IKDC grades were significantly different from autografts and early artificial ligaments, indicating that the short-term outcomes of early artificial ligaments were worse than autografts. The results of our research for early artificial ligaments were consistent with previous studies. It was not suggested to use early synthetic grafts including the LK artificial ligament and the LAD due to their poor follow-up outcomes.

The LARS artificial ligament was made of polyethylene terephthalate, divided in two parts (intra-articular part and extra-articular part) [34]. Intra-articular part was composed of longitudinal external rotation fibers without transverse fibers as an imitation of ACL anatomic structure while extra-articular part was woven by longitudinal and transverse fibers in order to avoid ligament deformation. Dericks et al. reported encouraging results in 220 cases of ACL reconstruction used LARS artificial ligament with a mean follow-up of 2.5 years [35]. In 2013, Parchi reported no case of complications and only one case of mechanical graft rupture after using LARS artificial ligament for ACL reconstruction at a mean follow-up of eight years [36]. In 2015, a study with a minimum follow-up of 10 years, showed almost half of the patients (8/18) were subjectively not satisfied with the surgical result using LARS artificial ligament [7]. The clinical outcomes were appealing at short-term but controversy at long-term [36–38]. In our research, 3 studies compared LARS artificial ligament with autografts, showing no significant difference in knee laxity, functions and the rate of complications [22, 25, 27]. The outcomes of LARS artificial ligament used in ACL reconstruction were appealing at least in short-term follow-up. Another new synthetic graft called PGA-Dacron graft, consisted of synthetic braided ligament made of 75% degradable PGA filaments and 25% non-degradable Dacron thread, showed a satisfied result compared to autograft including knee laxity, range of motion, patient-oriented questionnaires, muscle performance, degenerative changes of knee, and the rate of failure and complications [26].

Complications occurred in the autograft group were infection, patellofemoral pain, recurrent effusion and extension loss. In the synthetic graft group, complications included interference screw-related problems (pain and screw loosening), patellofemoral pain and extension loss. There were altogether 12 cases in the autograft group and 8 cases in the synthetic graft group. Extension loss was the most common complication in included studies and it might be associated with graft impingement and a formation of cyclops [39, 40]. Graft impingement was mainly caused by malposition of femoral bone tunnel and a “cyclops” was a fibrous nodule caused by proliferation of fibrovascular tissues similar to a healing scar.
ACL reconstruction [41, 42]. The synthetic grafts were located in a non-anatomic but isometric placement while the autografts were usually located in an anatomic placement. The results of complications showed no significant difference between these two location methods. Some studies documented that subjective outcomes were not correlated with objective outcomes including instrumented laxity test and clinical examination [43]. Among these included studies, three of them showed difference in objective parameters but no significant difference in patient-oriented outcomes [21, 22, 24]. Meanwhile, the opposite circumstance did not appear (similar in objective outcomes but different in subjective outcomes). Kraeutler et al. suggested that patient satisfaction is the most important measurable index for the outcomes of ACL reconstruction [13]. Only the overall IKDC grades showed better results in the autografts than in the early synthetic grafts and the rest indicators for patient satisfaction showed no significant difference between groups. However, it was still well recognized that a KT-1000 side-to-side difference of >5 mm was defined as a clinical failure [37]. Both objective and subjective outcomes should be considered for assessment of ACL reconstruction.

The limitations of this study were as follows: (1) Until now, there was still lack of high-quality RCT or large-scale multi-center retrospective comparable studies to prove the effectiveness of artificial ligaments compared to autografts. (2) The follow-up time was not sufficiently long for evaluation of ACL reconstruction. (3) In the included studies, the types of grafts used in ACL reconstruction were not the same (Hamstring tendon, BPTB, LK, LAD, LARS and PGA-Dacron). (4) The data included in the research did not cover all included studies due to the lack of relative data.

**Conclusions**

The outcomes of new generation of artificial ligaments are similar to autografts in terms of knee laxity, patient-oriented outcomes and the rate of complications at a short- to mid-term follow-up. However, the early artificial ligaments (LK, LAD) are not suggested for ACL reconstruction according to worse outcomes in knee laxity and functions compared to autografts.

**Abbreviations**

ACL: Anterior cruciate ligament; BPTB: Bone-patella tendon-bone; CI: Confidence interval; IKDC: International Knee Documentation Committee; ISRCTN: International Standard Randomised Controlled Trial Number; LAD: Ligament Augmentation Device; LARS: Ligament Advanced Reinforcement System; LK: Leeds-Keio; MD: mean difference; NOS: Newcastle-Ottawa scale; OR: Odds ratio; PGA-Dacron: polyglycolic acid Dacron; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT: Randomized controlled trial

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**Availability of data and materials**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Authors’ contributions**

JZ and ZC searched the databases and performed data extraction and quality assessment; JZ, HX and XW designed the study; JZ, ZC, CS, XC and LT analyzed the data and wrote the manuscript. JZ, ZC and CS revised the manuscript. All authors read and approved the final content of the manuscript.

**Ethical approval and consent to participate**

This article does not contain any studies with human participants or animals performed by any of the authors. There is no need for ethical approval and informed consents.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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