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META-ANALYSIS

# Meta-analysis of outcomes from drug-eluting stent implantation in infrapopliteal arteries

Ming-Xuan Li, Hai-Xia Tu, Meng-Chen Yin

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## Abstract

***BACKGROUND***

Percutaneous drug-eluting stent implantation (DESI) is an emerging and promising treatment modality for infrapopliteal artery diseases (IPADs). This systematic review and meta-analysis summarizes and quantitatively analyzes the outcomes of DESI in IPADs considering the hazard ratio (HR), which is a more accurate and appropriate outcome measure than the more commonly used relative risk and odds ratio.

***AIM***

To explore the superiority of drug-eluting stents (DESs) *vs* traditional treatment modalities for IPADs.

***METHODS***

The following postoperative indicators were the outcomes of interest: All-cause death (ACD)-free survival, major amputation (MA)-free survival, target lesion revascularization (TLR)-free survival, adverse event (AE)-free survival, and primary patency (PP) survival. The outcome measures were then compared according to their respective HRs with 95% confidence intervals (CIs). The participants were human IPAD patients who underwent treatments for infrapopliteal lesions. DESI was set as the intervention arm, and traditional percutaneous transluminal angioplasty (PTA) with or without bare metal stent implantation (BMSI) was set as the control arm. A systematic search in the Excerpta Medica Database (Embase), PubMed, Web of Science, and Cochrane Library was performed on November 29, 2022. All controlled studies published in English with sufficient data on outcomes of interest for extraction or conversion were included. When studies did not directly report the HRs but gave a corresponding survival curve, we utilized Engauge Digitizer software and standard formulas to convert the information and derive HRs. Then, meta-analyses were conducted using a random-effects model.

***RESULTS***

Five randomized controlled trials and three cohort studies involving 2639 participants were included. The ACD-free and MA-free survival HR values for DESI were not statistically significant from those of the control treatment ( $P > 0.05$); however, the HR values for TLR-free, AE-free, and PP-survival differed significantly [2.65 (95%CI: 1.56-4.50), 1.57 (95%CI: 1.23-2.01), and 5.67 (95%CI: 3.56-9.03), respectively].

*CONCLUSION*
Compared with traditional treatment modalities (*i.e.*, PTA with or without BMSI), DESI for IPADs is superior in avoiding TLR and AEs and maintaining PP but shows no superiority or inferiority in avoiding ACD and MA.

**Key Words:** Infrapopliteal; Drug-eluting stent; Below-the-knee; Meta-analysis; Hazard ratio



**Core Tip:** The utility of drug-eluting stents (DESs) for infrapopliteal artery diseases was explored using traditional percutaneous transluminal angioplasty with or without bare stent implantation as control. The results suggest that the DES is superior on multiple outcomes. The hazard ratio, which is most appropriate for various outcomes categorized as time-to-event data by type, was adopted as the outcome measure, rather than the relative risk or the odds ratio.

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## INTRODUCTION

Whether accompanied by femoropopliteal inflow disease or not, infrapopliteal artery disease (IPAD) is the primary cause of critical limb ischemia (CLI)[1,2]. Femoropopliteal-to-distal bypass surgery is considered the traditional treatment option for revascularization in IPADs[3-5]. Over the past few decades, minimally invasive percutaneous transluminal angioplasty (PTA) (*i.e.*, balloon dilatation) with or without bare metal stent implantation (BMSI) has been widely used, especially for patients with physical conditions that make it difficult for them to withstand open surgery or those lacking suitable distal arteries for bypass[6-10]. However, although this modality has a satisfactory technical success rate, it is associated with a significantly high risk of clinical failure due to lesion restenosis, even in the short term[11-13].

Drug-eluting stents (DESs) have demonstrated success in coronary artery diseases and have been widely demonstrated to maintain longer patency in femoropopliteal artery disease[14-16]. DES implantation (DESI) for IPADs was introduced over ten years ago[17-19]. Fusaro *et al*[20] reported the odds ratios (ORs) of some outcomes of DESI for IPADs *vs* control treatments in a meta-analysis published in 2013. Liu *et al*[21] reported the relative risks (RRs) in another meta-analysis published in 2017. However, similar to other intravascular therapies, almost all outcomes of concern after DESI are time-to-event data[22]; thus, the incidences of these outcomes will change significantly over time. In the PADI trial[23], the cumulative mortality at the one-year follow-up was 23.3% for DESI in IPADs and 62.3%[24] and 80.8%[25] at the 5- and 10-year follow-ups, respectively. Gratifyingly, an increasing number of clinical trials[24-27] have reported the outcomes of DESI for IPADs using the hazard ratio (HR), which is more appropriate for analyzing time-to-event data[28]. This makes it possible for us to perform a meta-analysis using this outcome measure.

## MATERIALS AND METHODS

### Study protocol

This review was registered with PROSPERO (CRD42022377456) in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework[29]. All data analyses were based on original studies; thus, no additional ethical approvals or participant consent forms were needed.

### Search strategy

The Excerpta Medica, PubMed, Web of Science, and Cochrane Library databases were searched on November 29, 2022. We searched without date limits for all relevant articles using "eluting", "stent", "limb" and all possible synonyms. All entry terms and search commands can be found in Supplementary material.

### Study selection

All references were imported into Endnote X9 for duplicate removal and a brief information review. Then, the full texts of all available articles that passed the preliminary screening were downloaded and read to identify those that could be

included in the final study. At this stage, the bibliographies and citations of the related articles were also screened for other potential articles.

We defined the HRs (DESI *vs* control treatments) with 95% confidence intervals (CIs) of the following five outcomes of IPADs as the primary outcome measures of interest: all-cause death (ACD)-free survival, major amputation (MA)-free survival, target lesion revascularization (TLR)-free survival, adverse event (AE)-free survival, and primary patency (PP) survival. Studies that simultaneously met the following criteria were included: 1) the study design was a randomized controlled trial (RCT) or cohort study; 2) the language of publication was English; 3) the target lesions of the human participants who underwent interventions were in infrapopliteal arteries demonstrating IPAD; 4) the number of participants in each arm was no less than 10; 5) DESI was conducted in one of the arms; and 6) at least one of the primary outcome measures of interest was directly reported, or at least one of the survival curves was provided. IPAD was defined as a disease caused by intraluminal atherosclerotic stenosis or occlusion of the popliteal artery below the tibial plateau level, anterior tibial artery, tibioperoneal trunk artery, posterior tibial artery, or peroneal artery. We did not limit the definition of the above five outcomes. Studies that did not meet the above criteria or only included complete duplicates of the outcome data available for extraction were excluded.

Two authors (Li MX and Tu HX) independently performed the search, title abstract filtering, and full-text review based on the above selection criteria. Any discrepancies were resolved by consensus.

### Data extraction

After identifying the studies for inclusion, we extracted the basic study and participant characteristics and the primary outcome measures. Directly reported adjusted HRs derived from multivariate Cox proportional hazard models were preferentially adopted and extracted. If HRs were absent but survival curves were present, we used Engauge Digitizer 11.3, an open-source software that can extract digital data from a graph, to transform the information in the curves and calculate the HRs[28,30,31]. Tierney *et al*[28] comprehensively summarized relevant statistical theories and provided an HR calculation spreadsheet (Excel format) with a preset calculation formula. We used this spreadsheet to calculate HRs instead of a manual calculation process. Data extraction was performed by a pair of independent authors (Li MX and Tu HX). Any discrepancies were resolved by consensus.

### Risk of bias assessment

We assessed the bias risk in the RCTs using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool[32]. This tool evaluates 5 domains: The randomization process, deviations from intended interventions, missing outcome data, outcome measurements, and reported result selection. The risk for each of the 5 domains and the overall risk is described as low, some concerns, or high. We assessed the risks of bias in cohort studies using the Cochrane Risk Of Bias In Nonrandomized Studies-of Interventions (ROBINS-I) tool[33]. This tool evaluates 7 domains: Confounding, participant selection, intervention classification, deviations from intended interventions, missing outcome data, outcome measurements, and reported result selection. The level of bias risk in each main study and overall was divided into five levels: low, moderate, serious, critical, and unclear. The highest risk level among all domains was adopted as the overall assessment result separately for each tool.

The risk of bias assessment was performed by a pair of independent authors (Li MX and Yin MC). When the two authors had different opinions on a certain assessment result, the worst opinion was adopted.

### Statistical analysis

Stata (Stata Corp, Texas, United States) version 16.0 was used for all statistical analyses. In each meta-analysis, we took the natural logarithms of the extracted HR value and the maximum and minimum 95%CI values per study and then included the three obtained variables in the "metan" command. To reduce error, a random-effects model rather than a fixed-effects model was used, regardless of the degree of heterogeneity among studies[34]. We corrected the degrees of freedom by restricted maximum likelihood estimation[35]. The calculation of the effect size (ES), *i.e.*, the pooled HR, of different study design types (RCTs or cohort studies) on individual outcomes was performed separately.

The formulas for the Cox proportional hazard model[36] (1) and the meta-analysis based on extracted or transformed data[28,30] (2,3) are as follows:

$$h(t,X) = h_0(t)exp(\beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_m x_m) \quad (1)$$

$$pooled\ lnHR = \sum\left(\frac{lnHR}{V}\right)/\sum\left(\frac{1}{V}\right) \quad (2)$$

$$V = [\ln(upper\ 95\%CI) - \ln(lower\ 95\%CI)]^2/(2*1.96)^2 \quad (3)$$

### Heterogeneity assessment and sensitivity analysis

The heterogeneity across the studies was assessed and reported as a percentage using the $I^2$ index value[37] and as a $P$ value using the Cochrane Q test of chi-square[38]. $I^2$ < 25% suggests low heterogeneity, 25% to 50% suggests moderate heterogeneity, and ≥ 50% suggests high heterogeneity. $P$ < 0.1 for the Q test suggests high heterogeneity, and ≥ 0.1 suggests low heterogeneity. Only the models without high heterogeneity in both tests were adopted.

Regardless of the degree of heterogeneity, checking calculations were performed by omitting the included studies one by one after a meta-analysis of at least three studies to analyze the sensitivity of the resulting model. A study was considered to introduce instability when the new pooled HR value obtained from the meta-analysis after its omission was distant from the previously obtained HR or beyond the 95%CI range.

### Publication bias assessment

The following methods of publication bias assessment were only performed if at least three studies were included in each meta-analysis. We assessed publication bias using Egger's test[39]. $P < 0.05$ indicated a high publication bias. Funnel plots [40] were also drawn. An asymmetric plot with the pooled HR value as the axis was considered to indicate high publication bias.

### Evidence quality grade assessment

After finishing the meta-analyses of all outcomes of interest, we used the Grading of Recommendations Assessment, Development and Evaluation system (GRADE)[41] to evaluate the qualities of evidence and make recommendations. Each result was graded as high, moderate, low, or very low. The results derived from the meta-analyses of RCTs were initially set as high, and the rating was lowered by a corresponding number of levels if the result appeared suspect in terms of overall bias, publication bias, inconsistency, imprecision, or indirectness. Those derived from the meta-analyses of cohort studies were initially set as very low, and the rating was raised by a corresponding number of levels if the result appeared suspect in terms of large magnitude of effect, dose-response gradient, or plausible confounding. The assessment was performed by a pair of independent authors (Li MX and Tu HX). When an assessment result was discordant and consensus could not be reached, the one with the lower grade was adopted. The higher assessment grade was adopted when two meta-analyses according to different study types were performed on the same outcome.

## RESULTS

### Selected studies and extracted data

We initially identified 1,234 articles by searching the 4 academic databases; 507 articles remained after removing duplicates. Thirteen articles were retained after title abstract filtering. After reviewing the full text, 5 papers[24,25,27,42,43] were retained, and 3 additional papers[26,44,45] obtained from the references in these articles were included in the final study. One study[25] was the continuation of another study[24] from the same RCT (PADI trial) over a longer follow-up period and reported an updated HR of ACD for 10 follow-up years. The PRISMA flowchart of study selection is shown in Figure 1.

All the control treatments adopted in the included studies could be divided into 2 categories: PTA with primary BMSI [26,27,42-44] and PTA with or without provisional BMSI[24,25,45]. In the recruitment or selection process, 2 studies[26,45] included a small number of non-CLIs, while the others included only CLIs. On grouping for outcome analysis, the 8 studies all followed the "intention-to-treat" principle rather than the "as-treated" principle. A total of 1493 patients who underwent DESI and 1146 who underwent control treatments were included. Their mean age exceeded 69 y, and the majority were male. The specific main characteristics of these studies and the baseline patient data are shown in Table 1. Some of the definitions of outcomes (other than ACD) in these studies were inevitably different. The specific definitions are shown in Table 2.

### Risks of bias

After assessment with the RoB 2.0 tool, the overall risk of bias was "high" in three[24,25,43] of the 5 included RCTs, and "some concerns" regarding this risk were found for the other two studies[26,45]. The 3 included cohort studies[27,42,44] were all at a "moderate" overall risk level after assessment by the ROBINS-I tool. The detailed final assessment results are shown in Table 3.

### ACD-free survival

One RCT[25] that directly reported the adjusted HR and another[43] that provided a K-M survival curve were included in a meta-analysis. The low heterogeneity suggested that there was no significant difference between DESI and control treatments in the risk of postoperative ACD [HR = 0.91 (95%CI: 0.38-2.18)] (Figure 2). A meta-analysis including 2 cohort studies[27,42] that directly reported the adjusted HRs and one[44] that provided a K-M survival curve yielded a similar result [HR = 1.15 (95%CI: 0.68-1.95)] with lower heterogeneity (Figure 3A). The sensitivity analysis suggested that this model had high stability (Figure 3B). The model had a P value of 0.137 by Egger's test, and its funnel plot was roughly symmetrical, indicating low publication bias (Figure 3C).

### MA-free survival

The results of a meta-analysis including 2 cohort studies[27,42] that directly reported the adjusted HRs and one[44] that provided a K-M survival curve suggested low heterogeneity and that there was no significant difference between the two arms in the risk of postoperative MA [HR = 1.20 (95%CI: 0.84-1.71)] (Figure 4A). The stability of the model was unsatisfactory (Figure 4B), but the publication bias was low ($P = 0.350$ for Egger's test) (Figure 4C). Only one result[24] was available among the included RCTs, which was a directly reported adjusted HR [1.64 (95%CI: 0.74-3.70)], similar to the above findings.

### TLR-free survival

The 3 included cohort studies[27,42,44] all directly reported the adjusted HRs of TLR-free survival. A primary meta-analysis yielded a result favoring DESI [HR = 1.93 (95%CI: 1.16-3.22)] (Figure 5A). However, the model was highly heterogeneous ($I^2 = 56.3\%$) and was not adopted. We conducted meta-analyses of pairwise combinations of the 3 studies

**Table 1 Main characteristics and baselines of the included studies**

| Ref. | Design | Coutry/Registry | Enrollment period | Drug on DES | Control | Optimal stenting[a] | Num of patients | Mean age (yr) | Male (%) | Num of limbs | Num of arteries | Num of lesions | Median RC | Mean LRD (mm) | Mean LL (mm) | CTO (%) | Follow up period (yr)[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Siablis *et al*[42], 2009 | PCS | Greece | NA | S | PTA+BMSI | N *vs* N | 62 *vs* 41 | 69 *vs* 72 | 71 *vs* 90 | 75 *vs* 47 | NA | 153 *vs* 77 | 5 *vs* 5 | NA | 55 *vs* 45 | 25 *vs* 35 | 1 |
| Karnabatidis *et al*[44], 2011 | ACS | Greece | 2006-2009 | S | PTA+BMSI | Y *vs* N | 47 *vs* 34 | 71 *vs* 71 | 74 *vs* 82 | 51 *vs* 36 | 75 *vs* 57 | 102 *vs* 72 | 4 *vs* 5 | NA | 76 *vs* 77 | 17 *vs* 35 | 1 |
| Scheinert *et al* [45], 2012 | RCT | ACHILLES | 2008-2010 | S | PTA±BMSI | Y *vs* N | 99 *vs* 101 | 72 *vs* 74 | 68 *vs* 75 | NA | NA | 113 *vs* 115 | 4 *vs* 4 | 2.6 *vs* 2.6 | 27 *vs* 27 | 81 *vs* 75 | 1 |
| Rastan *et al*[26], 2012 | RCT | Germany | 2006-2008 | S | PTA+BMSI | Y *vs* Y | 82 *vs* 79 | 73 *vs* 72 | 68 *vs* 65 | NA | NA | 82 *vs* 79 | 4 *vs* 3 | 3.0 *vs* 3.0 | 30 *vs* 31 | 23 *vs* 22 | 3 |
| Bosiers *et al*[43], 2012 | RCT | DESTINY | 2008-2009 | E | PTA+BMSI | Y *vs* Y | 74 *vs* 66 | 75 *vs* 76 | 61 *vs* 58 | 78 *vs* 76 | 78 *vs* 76 | 78 *vs* 76 | 4.5 *vs* 5 | 3.0 *vs* 2.9 | 16 *vs* 19 | 15 *vs* 17 | 1 |
| Spreen *et al*[24], 2017 | RCT | PADI | 2007-2013 | P | PTA±BMSI | Y *vs* N | 73 *vs* 64 | 74 *vs* 73 | 67 *vs* 73 | 74 *vs* 66 | NA | 121 *vs* 91 | 5 *vs* 5 | 2.9 *vs* 2.9 | 21 *vs* 23 | NA | 3 |
| Konijn *et al*[25], 2020 | RCT | PADI | 2007-2013 | P | PTA±BMSI | Y *vs* N | 73 *vs* 64 | 74 *vs* 73 | 67 *vs* 73 | 74 *vs* 66 | NA | 121 *vs* 91 | 5 *vs* 5 | 2.9 *vs* 2.9 | 21 *vs* 23 | NA | 10 |
| Zuzek *et al*[27], 2022 | RCS | USA | 2016-2017 | NA | PTA+BMSI | NA | 1056 *vs* 761 | 72 *vs* 72 | 59 *vs* 64 | NA | NA | NA | 5 *vs* 5 | NA | NA | NA | 0.5 |

[a]DES implantation was performed regardless of whether predilatation was performed or the outcome of predilatation.

[b]Approximate mean. The data variables of double arms are presented in the form of "DES vs control".

PCS: Prospective cohort study; ACS: Ambispective cohort study; RCT: Randomized controlled trial; RCS: Retrospective cohort study; NA: Not available; DES: Drug-eluting stent; S: Sirolimus; E: Everolimus; P: Paclitaxel; PTA: Percutaneous transluminal angioplasty; BMSI: Bare metal stent implantation; N: No; Y: Yes; Num: Number; RC: Rutherford classification; LRD: Lesion reference diameter; LL: Lesion length; CTO: Chronic total occlusion.

and obtained a model with low heterogeneity[42,44], which suggested a similar result to that described above [HR = 2.65 (95%CI: 1.56-4.50)] (Figure 5B). Among the RCTs included, only[43] had an available result, *i.e.*, a K-M survival curve. From this curve, we extracted and converted a result [HR = 2.07 (95%CI: 0.78-5.52)], and the findings indicated no significant difference between the two arms.

### *AE-free survival*

The results of a meta-analysis including 2 RCTs[24,26] that directly reported the adjusted HRs and one[45] that provided a K-M survival curve suggested low heterogeneity and that DESI better prevented AEs postoperatively [HR = 1.57 (95%CI: 1.23-2.01)] (Figure 6A). The stability of the model was satisfactory (Figure 6B), and the publication bias was low ( $P$ = 0.917 for Egger's test) (Figure 6C). Only one result[24] of the included cohort studies was available, which was an adjusted HR [2.19 (95%CI: 1.16-4.13)] that was directly reported and similar to above.

**Table 2 Definitions of the outcomes during follow-up extracted from the included studies**

| Ref. | ACD | MA | TLR | AE | PP |
|---|---|---|---|---|---|
| Siablis *et al*[42], 2009 | All-cause death | Amputation above the ankle | Repeated revascularization on the target lesion prompted by deterioration of limb ischemia | NA | Absence of repeated intervention and occlusion detected by angiography in the target lesion |
| Karnabatidis *et al*[44], 2011 | Same as the top[a] | NI[a] | Same as the top | ACD, or MA, or TLR | Same as the top |
| Scheinert *et al*[45], 2012 | NA | NA | NA | ACD, or MA, or TLR, or RC ≥ 4[a] | NA |
| Rastan *et al*[26], 2012 | NA | NA | NA | ACD, or MA, or target vessel revascularization, or myocardial infarction | NA |
| Bosiers *et al*[43], 2012 | Same as the top[a] | NA | NI* | NA | Absence of ≥ 50% binary ISR detected by angiography[a] |
| Spreen *et al*[24], 2017 | NA | Amputation above the ankle | NA | MA, or target limb revascularization | NA |
| Konijn *et al*[25], 2020 | Same as the top | NA | NA | NA | NA |
| Zuzek *et al*[27], 2022 | Same as the top | Amputation above the transmetatarsal | Same as the top | NA | NA |

[a]Data extracted from survival curve presented in the article and thus transformed. ACD: All-cause death; NA: Not available; MA: Major amputation; NI: No information; TLR: Target lesion revascularization; AE: Adverse event; RC: Rutherford classification; PP: Primary patency; ISR: In-stent restenosis.

**Table 3 Risk bias assessment results of included studies**

| **The domains in RoB 2.0a for RCTs** | **Scheinert *et al*[45], 2012** | **Rastan *et al*[26], 2012** | **Bosiers *et al*[43], 2012** | **Spreen *et al*[24], 2017** | **Konijn *et al*[25], 2020** |
|---|---|---|---|---|---|
| 1 Randomisation process | Low | Low | Low | Low | Low |
| 2 Deviations from the intended interventions | Low | Low | Low | Low | Low |
| 3 Missing outcome data | Some concerns | Some concerns | High | High | High |
| 4 Measurement of the outcome | Low | Low | Low | Low | Low |
| 5 Selection of the reported result | Low | Low | Low | Low | Low |
| 6 Overall | Some concerns | Some concerns | High | High | High |
| **The domains in ROBINS-Ib for cohort studies** | **Siablis *et al*[42], 2009** | **Karnabatidis *et al*[44], 2011** | **Zuzek *et al*[27], 2022** | | |
| 1 Confounding | Low | Moderate | Moderate | | |
| 2 Selection of participants | Low | Low | Low | | |
| 3 Classification of interventions | Low | Low | Low | | |
| 4 Deviations from intended interventions | Low | Low | Moderate | | |
| 5 Missing outcome data | Moderate | Moderate | Moderate | | |
| 6 Measurement of outcomes | Moderate | Moderate | Moderate | | |
| 7 Selection of the reported result | Low | Low | Low | | |
| 8 Overall | Moderate | Moderate | Moderate | | |

[a]The risk is graded into 3 levels: low: some concerns: and high.
[b]The risk is graded into 5 levels: low: moderate: serious: critical: and no information. RoB: Risk of bias tool; RCT: Randomized controlled trial; ROBINS-I: Risk of bias in non-randomised studies-of interventions.

### *PP survival*

Two cohort studies[42,44] were included in a meta-analysis, both of which directly reported the adjusted HRs. The results of the analysis suggested that the DESI performed better in maintaining PP postoperatively [HR = 5.67 (95%CI: 3.56-9.03)] (Figure 7). Among the RCTs included, only one[43] had an available result, that is, a K-M survival curve. We extracted and converted a result from this curve [HR = 1.68 (95%CI: 0.88-3.94)], and no significant difference was indicated between the two arms.

### *Evidence quality grade*

Only ACD-free survival among the 5 outcomes of interest necessitated 2 meta-analyses due to different study types. We adopted a higher evidence quality grade, *i.e.*, moderate, after the assessment. The detailed assessment results are shown in Table 4.

## DISCUSSION

This meta-analysis including 5 RCTs and 3 cohort studies systematically reviewed and analyzed multiple follow-up outcomes of DESI performed in infrapopliteal arteries. The results revealed that DESI showed no superiority in comparison with the control treatments in terms of ACD-free and MA-free survival; however, DESI demonstrated statistically significant advantages in terms of TLR-free, AE-free, and PP survival. Studies[46-49] have extensively demonstrated the superiority of stents eluted with antiproliferative drugs, such as paclitaxel, sirolimus, and everolimus, in coronary arteries with similar luminal diameters to infrapopliteal arteries. It is unsurprising that such promising stents have gradually been used in lower leg lesions. As traditional revascularization modalities[6-10], BMSI and PTA are currently the most commonly used control treatments in related studies. The PADI trial[25] resulted in survival curves up to the 10-year follow-up of DESI for IPADs with PTA ± BMSI as a control. Zuzek *et al*[27] reported survival curves (DESI *vs* BMSI) for multiple outcomes in a cohort study including 1817 participants with IPAD. In recent years, meta-analyses of relevant con-trolled studies have also been published. In these analyses, few[21,50] reported different pooled ESs after grouping by follow-up period; most[2,51-53] only reported those at the one-year follow-up, and some[20,54] even directly pooled the ESs among different follow-up periods. The outcomes of interest for these analyses were, without exception, the cumulative postoperative inci-dences of some events at a given follow-up moment, which were considered static indicators. However, as described in the "Introduction" section, our outcomes of interest are all time-to-event data[22]. For example, the ACD of a PADI patient is almost impossible to determine on the first postoperative day of DESI but will occur over time. Unlike the RR or data [which can only evaluate the cumulative risk at a certain period, the HR derived from a proportional hazards regression model (such as the Cox model) including the time variable is more appropriate for assessing the risks of relevant outcomes[28,36]. However, no relevant meta-analyses using HR as the outcome measure were found. In addition, when using the HR for meta-analysis, ESs from studies with different follow-up periods can be included in the same pooled analysis without grouping, and some rare studies with long follow-up periods can also be included (*e.g.*, the PADI trial[25] seems to be the only control study that has reported the relevant outcomes at the 10-year follow-up). This approach is beneficial to expand the sample size and increase the statistical power.

In addition to the 5 RCTs, we also included 3 cohort studies. The inherent flaws in study design that render cohort studies more at risk of bias than RCTs may call them into question[41]. However, the included 3 cohort studies provided more data that could be used for meta-analysis than the above 5 RCTs. In addition, after assessment, no critical risk of bias was found among these cohort studies, and the evidence qualities of the resulting meta-analyses were mostly satisfactory (2 high, 1 medium, and only 1 Low).

We found that the most prominent risks of all the included studies were all from the domain of missing outcome data. Due to very limited information, we could not determine the specific reasons for missing data in each study. However, we believe that censoring due to ACD, which is impossible to completely avoid, is a common and important reason for this type of bias risk in these studies. In addition to the general doubts in the above domain, the risks in other domains of the included studies were not serious after assessment, which is why we did not exclude any of the 8 studies based on the overall assessment results.

The results of statistical analyses are discussed below. First, the two meta-analyses on ACD-free survival both resulted in the same conclusion: DESI for IPADs has no advantages in avoiding postoperative ACD *vs* the control treatments, increasing persuasiveness. Second, a meta-analysis on MA-free survival resulted in a similar conclusion to that described above: DESI has no advantages in avoiding postoperative MA. The model derived from this analysis was considered less stable after the sensitivity analysis. This instability was caused by a study favoring DES and had a very narrow 95%CI range of HR, accounting for over 80% of the weight individually in the pooled analysis[27]. According to the available data, this study was the only retrospective study among the included studies, and its sample size seemed to be significantly larger than that of other studies. However, this is an insufficient explanation for the differing result. It is also slightly regrettable that because the data were derived from cohort studies rather than RCTs and there was only 1 add-on in the assessment, this conclusion was the only one of the 5 recommended conclusions to be assessed as low-quality. Third, after excluding one study, the meta-analysis on TLR-free survival with lower heterogeneity indicated that DESI has significant advantages in avoiding postoperative TLR [HR = 2.65 (95%CI: 1.56-4.50)]. The study that brought major heterogeneity was again the one mentioned above[27], and its result was also different (*i.e.*, no tendency). Fourth, after the meta-analysis on AE-free survival, we concluded that DESI has significant advantages in avoiding postoperative AE [HR = 1.57 (95%CI: 1.23-2.01)]. Similarly, one study[45] was not statistically consistent with the other two[24,26], and the final

**Table 4 Evidence quality grade assessment of pooled outcomes of interest**

| Outcome | Source of data | Num of participants | Pooled HR (DES *vs* control) | Certainty of the evidence (GRADE)[a] | Alteration to initial rating |
|---|---|---|---|---|---|
| ACD-free survival | 2 RCTs | 277 | 0.91 (95%CI: 0.38-2.18) | Moderate | -1[b] |
| ACD-free survival | 3 cohort studies | 2001 | 1.15 (95%CI: 0.68-1.95) | Low | +1[c] |
| MA-free survival | 3 cohort studies | 2001 | 1.20 (95%CI: 0.84-1.71) | Low | +1[c] |
| TLR-free survival | 2 cohort studies | 184 | 2.65 (95%CI: 1.56-4.50) | High | +3[d] |
| AE-free survival | 3 RCTs | 498 | 1.57 (95%CI: 1.23-2.01) | Moderate | -1[b] |
| PP survival | 2 cohort studies | 184 | 5.67 (95%CI: 3.56-9.03) | High | +3[d] |

[a]High certainty: We are very confident that the true effect lies close to that of the estimate of the effect; moderate certainty: We are moderately confident in the effect estimate; low certainty: Our confidence in the effect estimate is limited; very low certainty: We have very little confidence in the effect estimate.
[b]The reason for lowering rating was a suspect of overall bias.
[c]The reason for raising rating was a consideration of plausible confounding.
[d]The reason for raising rating was a consideration of large magnitude of effect, dose-response gradient, and plausible confounding. ACD: All-cause death; MA: major amputation; TLR: Target lesion revascularization; AE: Adverse event; PP: Primary patency; RCT: Randomized controlled trial; Num: number; HR: Hazard ratio; CI: Confidence interval; GRADE: Grading of recommendations assessment: Development and evaluation.

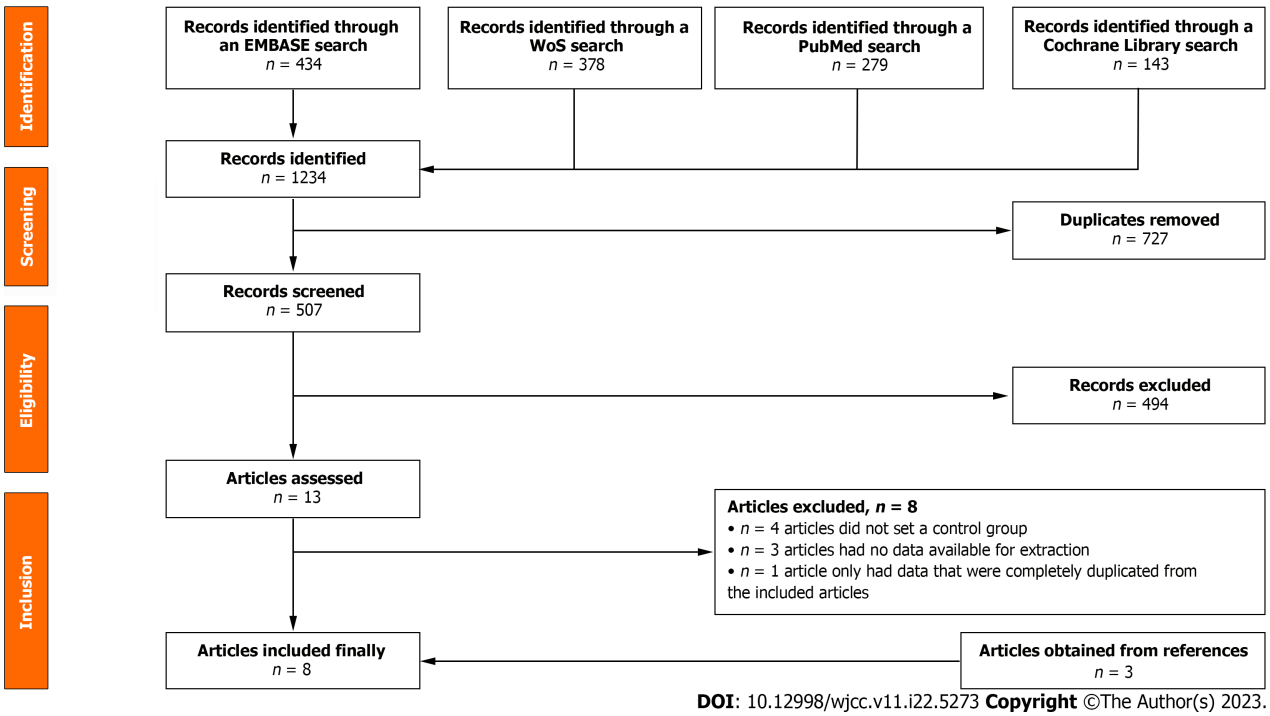


**Figure 1 PRISMA flowchart.** PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

result was "no tendency". The biggest evident discrepancy in that study is that its follow-up period was only 1 year, while the others involved a 3-year follow-up. Thus, AE-free survival and other IPAD outcomes potentially do not develop linearly, and the advantages of DESI gradually emerge with time. Fifth, the meta-analysis on PP survival revealed that DESI has significant advantages in maintaining postoperative PP survival [HR = 5.67 (95%CI: 3.56-9.03)]. The high HR value reflects the great ad-vantages of DES in this respect.

This study has some limitations. First, the sample size is small, which reduces the persuasiveness of the results. To date, the number of controlled studies on DESI for IPADs is still limited in comparison with those on DESI for femoro-popliteal artery dis-eases[55-66]. DESs specific for femoropopliteal arteries, such as Zilver PTX (Cook Medical, United States) and Eluvia (Boston Scientific, United States). Have been used in many countries. However, a dedicated infrapopliteal artery stent is absent, at least in China, and a coronary stent is used. Second, the definitions of some outcomes of interest slightly differed among the included studies. For example, one study[26] regarded myocardial infarction as an AE, while others with relevant data did not; some studies[43,44] did not even explain the definitions of certain outcomes, increasing the risks of error in the results. Third, to bring as many studies as possible into the analyses, we extracted data from the survival curves given in some of the studies[43-45]. Although sufficient evidence[28,30,31]

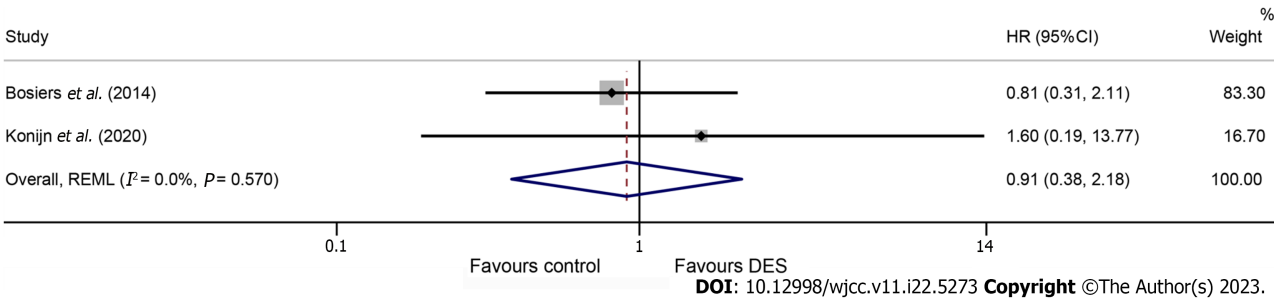


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**Figure 2 Forest plot of all-cause death -free survival derived from pooling 2 randomized controlled trials (random effects model).** HR: Hazard ratio; CI: Confidence interval; REML: Restricted maximum likelihood; DES: Drug-eluting stent.

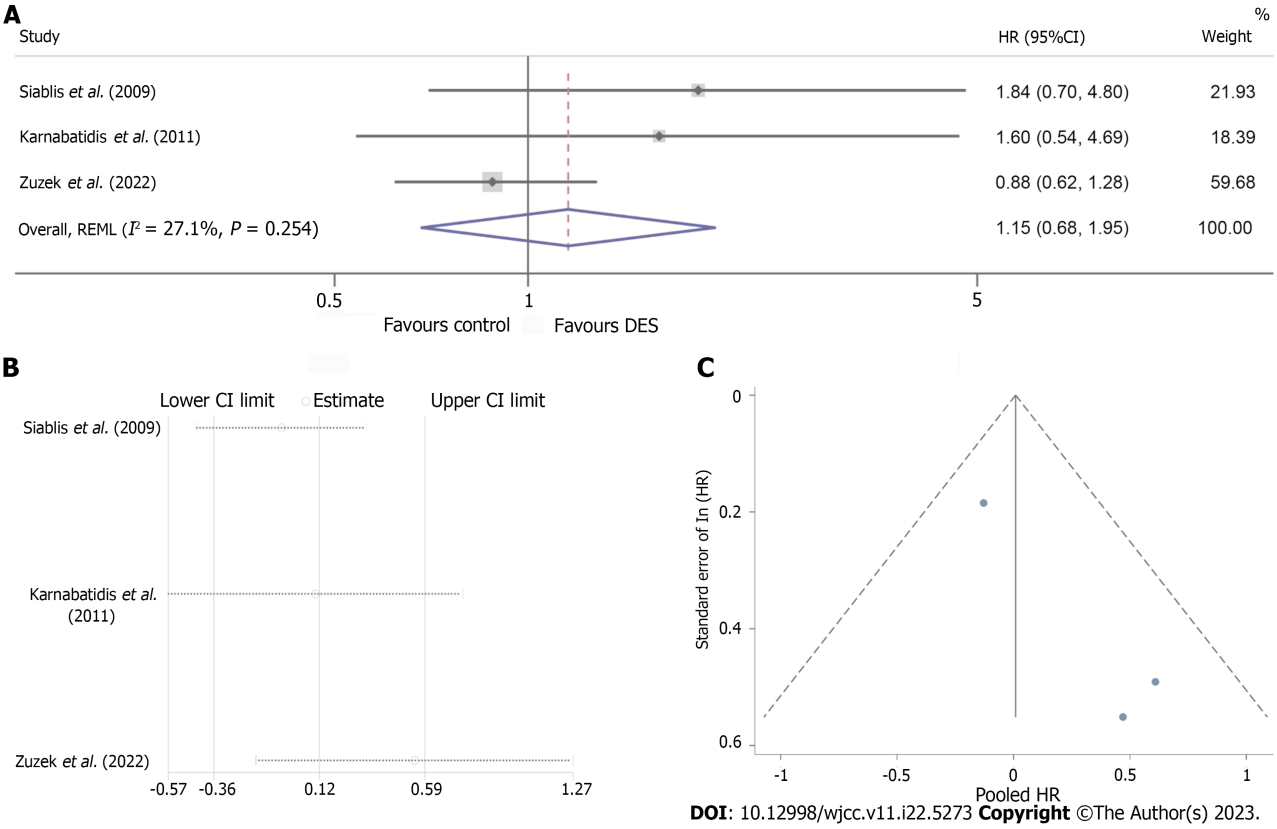


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**Figure 3 All-cause death -free survival.** A: Forest plot derived from pooling 3 cohort studies (random effects model); B: Sensitivity analysis of the model assuming that each study was omitted separately [ln(HR)]; C: Funnel plot with pseudo 95% confidence limits. HR: Hazard ratio; CI: Confidence interval; REML: Restricted maximum likelihood; DES: Drug-eluting stent; ACD: All-cause death.

supports the rationality of this approach, it is, after all, a recalculation and not a direct HR, unlike that in the other studies, which inevitably increases the error.

## CONCLUSION

Compared with traditional treatment modalities (PTA with or without BMSI), DESI for IPADs is significantly superior in avoiding TLR and AEs and maintaining PP survival, while showing no superiority or inferiority in terms of ACD-free and MA-free survival. In conclusion, DES is a good option for IPADs to maintain efficacy for long periods.

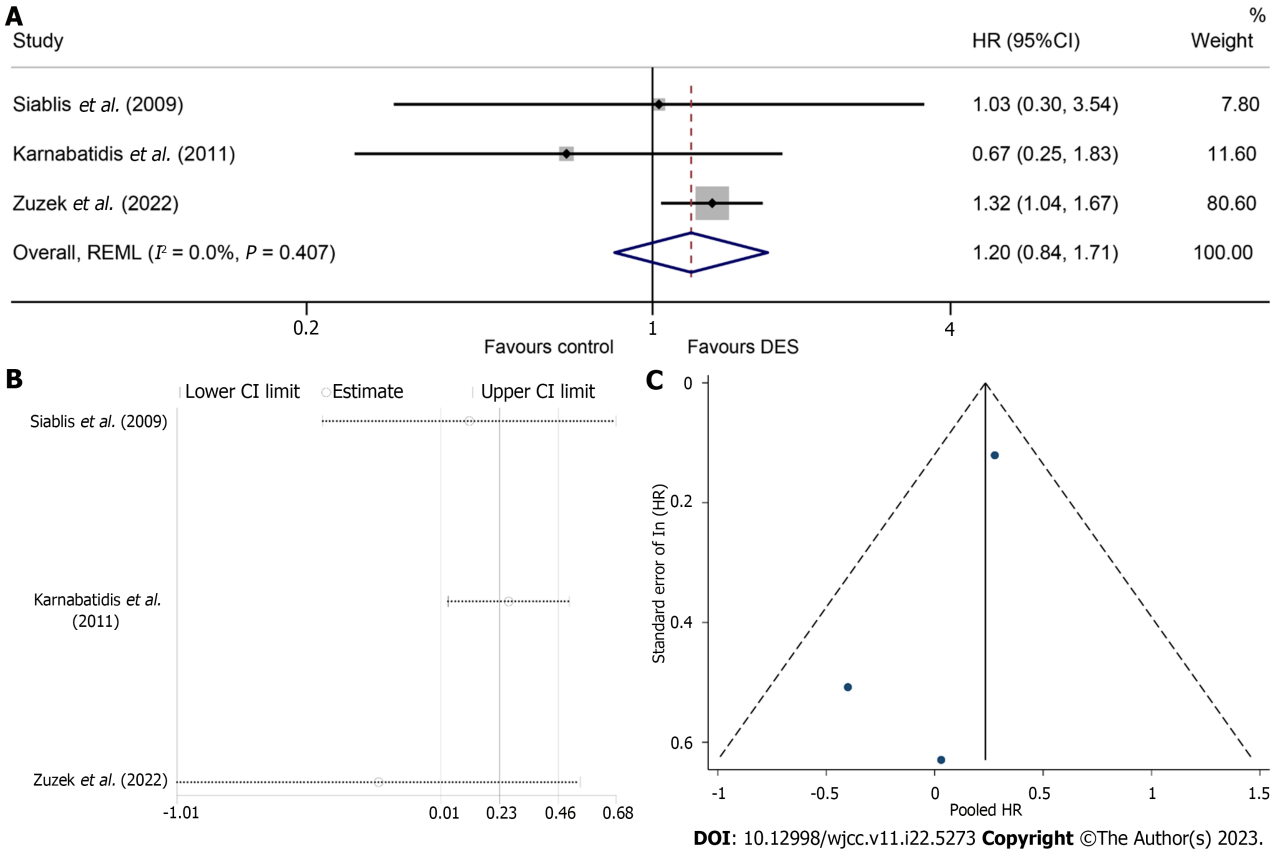


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**Figure 4 Major amputation -free survival.** A: Forest plot derived from pooling 3 cohort studies (random effects model); B: Sensitivity analysis of the model assuming that each study was omitted separately [ln(HR)]; C: Funnel plot with pseudo 95% confidence limits. HR: Hazard ratio; CI: Confidence interval; REML: Restricted maximum likelihood; DES: Drug-eluting stent.

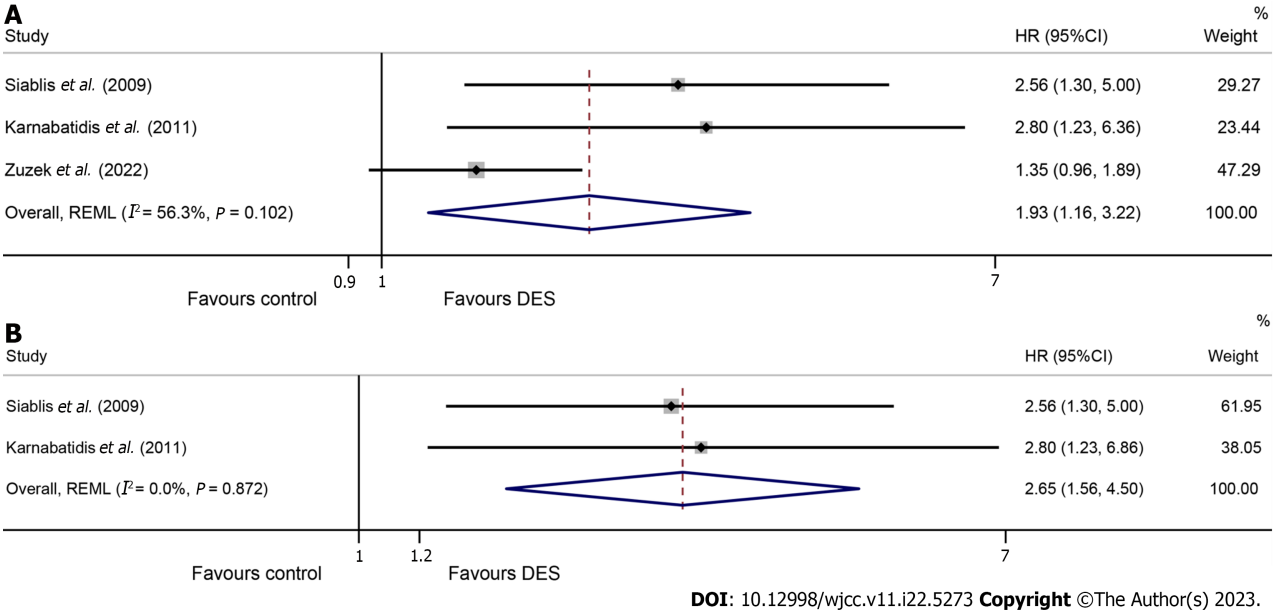


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**Figure 5 Target lesion revascularization -free survival.** A: Forest plot with high heterogeneity derived from pooling 3 cohort studies (random effects model); B: Forest plot with low heterogeneity derived from pooling 2 cohort studies (random effects model). HR: Hazard ratio; CI: Confidence interval; REML: Restricted maximum likelihood; DES: Drug-eluting stent; TLR: Target lesion revascularization.

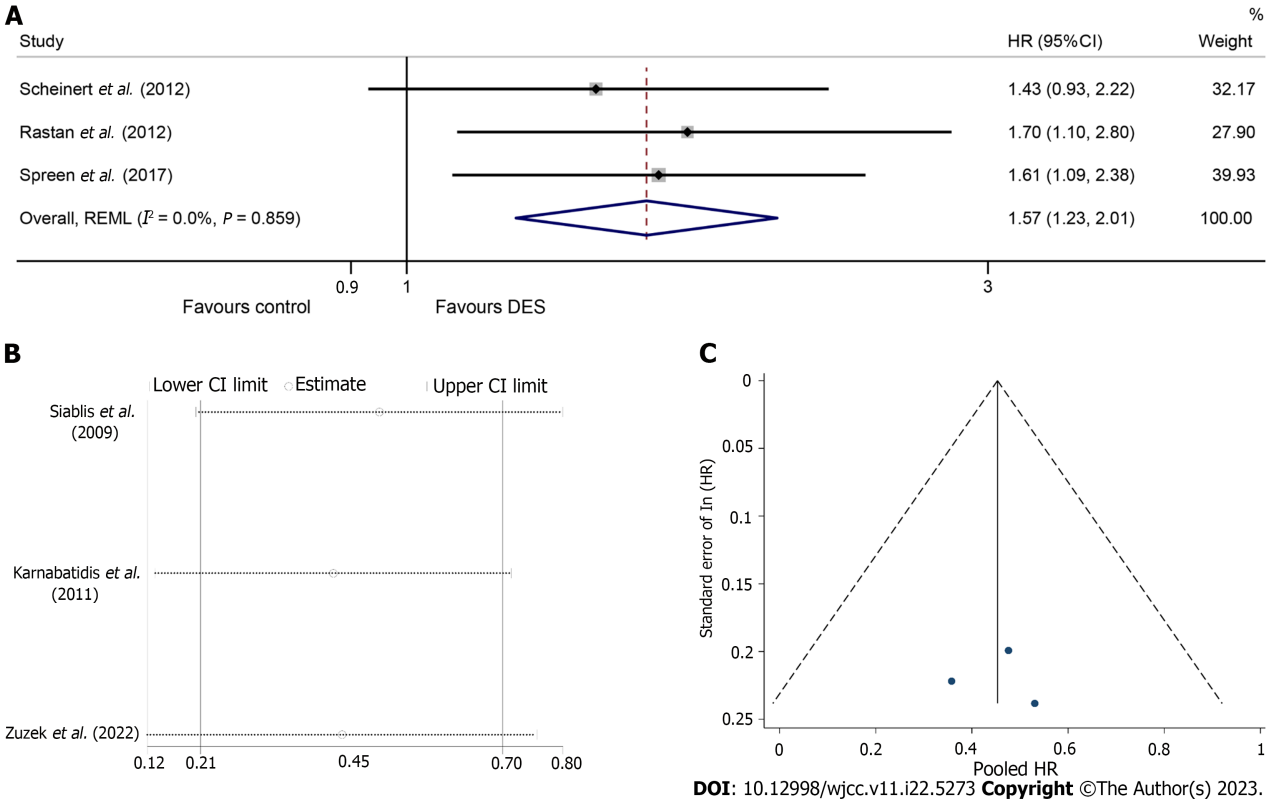


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**Figure 6 Adverse event -free survival.** A: Forest plot derived from pooling 3 cohort studies (random effects model); B: Sensitivity analysis of the model assuming that each study was omitted separately [ln(HR)]; C: Funnel plot with pseudo 95% confidence limits. HR: Hazard ratio; CI: Confidence interval; REML: Restricted maximum likelihood; DES: Drug-eluting stent.

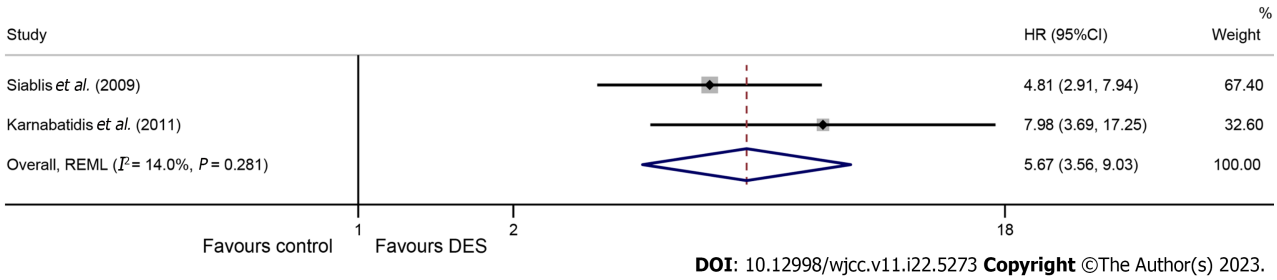


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**Figure 7 Forest plot of primary patency survival derived from pooling 2 cohort studies (random effects model).** HR: Hazard ratio; CI: Confidence interval; REML: Restricted maximum likelihood; DES: Drug-eluting stent.

## ARTICLE HIGHLIGHTS

### *Research background*

Whether accompanied with femoropopliteal inflow disease or not, infrapopliteal artery disease (IPAD) is the primary cause of critical limb ischemia. In the past few decades, minimally invasive percutaneous transluminal angioplasty (PTA) with or without bare metal stent implantation (BMSI) has been widely used.

### *Research motivation*

However, although this treatment has satisfactory technical success rate, it still has a significantly high risk of clinical failure caused by lesion restenosis even in the short term.

### *Research objectives*

In order to more accurately evaluate the efficacy of drug-eluting stents (DES) implantation for IPADs, we performed this systematic review and meta-analysis.

### *Research methods*

After extensive retrieval of major databases, the hazard ratio (HR) is used as the outcome measure for extraction or conversion, and the meta analyses for multiple outcomes of interest were performed.

### *Research results*

Five randomized controlled trials and three cohort studies involving 2639 participants totally were included. Compared with the control arm (PTA and BMSI), the HR values of the DES implantation on all- cause death -free survival and major amputation -free survival were not statistically significant ($P > 0.05$), but the HR values on target lesion revascularization -free survival, adverse event -free survival, and primary patency -survival were 2.65 (95%CI: 1.56-4.50), 1.57 (95%CI: 1.23-2.01), and 5.67 (95%CI: 3.56-9.03), respectively.

### *Research conclusions*

In our conclusion, DES is a good option for IPADs to maintain efficacy for a long time.

### *Research perspectives*

DES is a highly anticipated therapeutic device. We believe that there will be more and more randomized controlled trials about its application for IPADs in the future.

## FOOTNOTES

**Author contributions:** Li MX designed the study; Li MX and Tu HX performed the article search, data extraction, and evidence quality assessment; Li MX and Yin MC performed the risk of bias assessment of the studies; Li MX performed the data analyses and manuscript writing; Tu HX reviewed the article independently and made minor revisions after consultation with Li MX; All the authors read and gave final approval of the version to be submitted; Tu HX is the guarantor of the review.

**Conflict-of-interest statement:** The authors declare that they have no conflicts of interest to report.

**PRISMA 2009 Checklist statement:** The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.



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