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Review

Clinical results of biologic prosthesis: A systematic review and meta-analysis of comparative studies

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HIGHLIGHTS

- This study summarized the gap of knowledge of clinical outcome when compare with biologic prosthesis and PTFE.
- This first meta-analysis was shown clearly about results and high performance of study were collected.
- For the conclusion, high efficacy of alternative treatment was shown, however, further study needed to confirm the results.

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ABSTRACT

Background: Biologic prosthesis (BP) has been reported as a safe alternative to polytetrafluoroethylene (PTFE) in vascular reconstruction. However, efficacy of BP remains controversial. We, therefore, conducted a systematic review to summarize previous available evidences comparing the BP and PTFE in terms of clinical outcomes.

Materials and methods: A literature search of the MEDLINE and Scopus was performed to identify comparative studies reporting outcomes of BP, PTFE, and/or autologous veins graft (VG) in vascular access for hemodialysis or femoropopliteal bypass. The outcome of interest was graft patency. Two reviewers independently extracted data. Meta-analysis with a random-effect model was applied to pool a risk ratio (RR) across studies.

Results: Among 584 articles identified, 11 studies (4 randomized controlled trials (RCT) and 7 cohorts) comprising 2627 patients were eligible for pooling. Seven studies compared BP with PTFE and 3 studies compared PTFE with VG. Among BP vs PTFE, pooling based on 3 RCTs yielded the pooled RR of 1.54 (95% CI: 1.10, 2.16), indicating 54% higher graft patency in VG than PTFE. Adding the 7 cohorts in this pooling yield similar results with the pooled RR of 1.29 (95% CI: 1.15, 1.45). The pooled RR of graft patency for BP vs VG was 0.74 (95% CI, 0.55, 1.00), indicating 26% lower graft patency in BP than VG.

Conclusions: Our first meta-analysis indicated that the biosynthetic prosthesis might be benefit over PTFE by increasing graft patency. An updated meta-analysis or a large scale randomized control trial is required to confirm this benefit.

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1. Introduction

Maintenance of well-functioning vascular graft is a major challenge in continuing care of patients who have vascular access for hemodialysis and vascular bypass procedures. Different types of vascular grafts are available for dialysis access settings and peripheral vascular reconstructions [1]. The greater saphenous vein remains the conduit of choice for vascular procedure and native arteriovenous fistula (AVF) is recommended as the first choice of vascular access for hemodialysis [2]. However, autologous vein graft and access are not feasible in a significant number of patients. The use of prosthesis conduit to create a bridging access graft and vascular reconstruction are the best alternative. The expanded polytetrafluoroethylene (PTFE) was the most commonly used vascular prosthesis with limited graft patency and significant number of complications [3]. Biologic prosthesis (BP) has been reported as a safe alternative to polytetrafluoroethylene (PTFE) in vascular reconstruction [4–14]. However, efficacy of BP remains controversial. We, therefore, conducted a systematic review to summarize previous available evidences comparing the BP and PTFE in terms of graft patency.

2. Methods

A literature search of the MEDLINE and Scopus was performed from January 1946 to December 2015. The search strategy is described in appendix 1.

2.1. Inclusion criteria

Studies were included in the review if they met with the following criteria:

- Had study design as randomized controlled trial or cohort study
- Studied in adult patients aged 18 years or older
- Patients who received vascular access procedure for hemodialysis or femoropopliteal bypass
- Compared clinical outcomes between biologic prosthesis (BP), polytetrafluoroethylene (PTFE), and/or autologous veins graft (VG):
- Had at least on of following clinical outcomes: graft patency, graft survival, graft thrombosis, graft infection.

The reference lists of all relevant studies were also reviewed. If studies were duplicated reports, the one with the most complete data was chosen. For studies which reported insufficient data, the corresponding authors were contacted and invited to provide more information. Two attempts were made to contact authors and those who did not respond were excluded from the review.

2.2. Outcomes

The outcome of interest was graft patency which was detected by audible Doppler signal or duplex ultrasound. Primary graft patency was analyzed up to the first graft thrombosis while patency following graft revision procedures was used as secondary patency.

2.3. Data extraction

Two reviewers (CW and BS) independently extracted the data from each study using a standard data extraction form. Information extracted included general data (i.e. author, year of publication, journal), study characteristics (i.e. study design, setting), patient characteristics (i.e. age, underlying diseases, surgical procedures, type of prosthesis, follow up period), and outcome as described above. Any disagreement was discussed and resolved by consensus with the third party (SR).

2.4. Risk of bias assessment

The quality of studies was independently assessed by CW, BS, and SH on the basis of representativeness of studied subjects, information bias (i.e., ascertainment of outcome and surgical technique), and confounding bias [15] (appendix 2). For the randomized controlled trial (RCT) study, the assessment was done using established tools recommended by the Cochrane library [16]. Each item was graded as “yes” for low risk of bias, “no” for high risk of bias, and “unclear” if there was insufficient information to judge [16]. Any disagreement between the reviewers was discussed and resolved by consensus.

2.5. Statistical analysis

Data from RCTs and cohort studies were pooled separately. The risk ratio (RR) of graft patency for each included study was estimated. The heterogeneity of RRs across studies was assessed using Cochran's Q test and the degree of heterogeneity was quantified using the I^2 statistic. If the heterogeneity was significant or $I^2 > 25\%$,

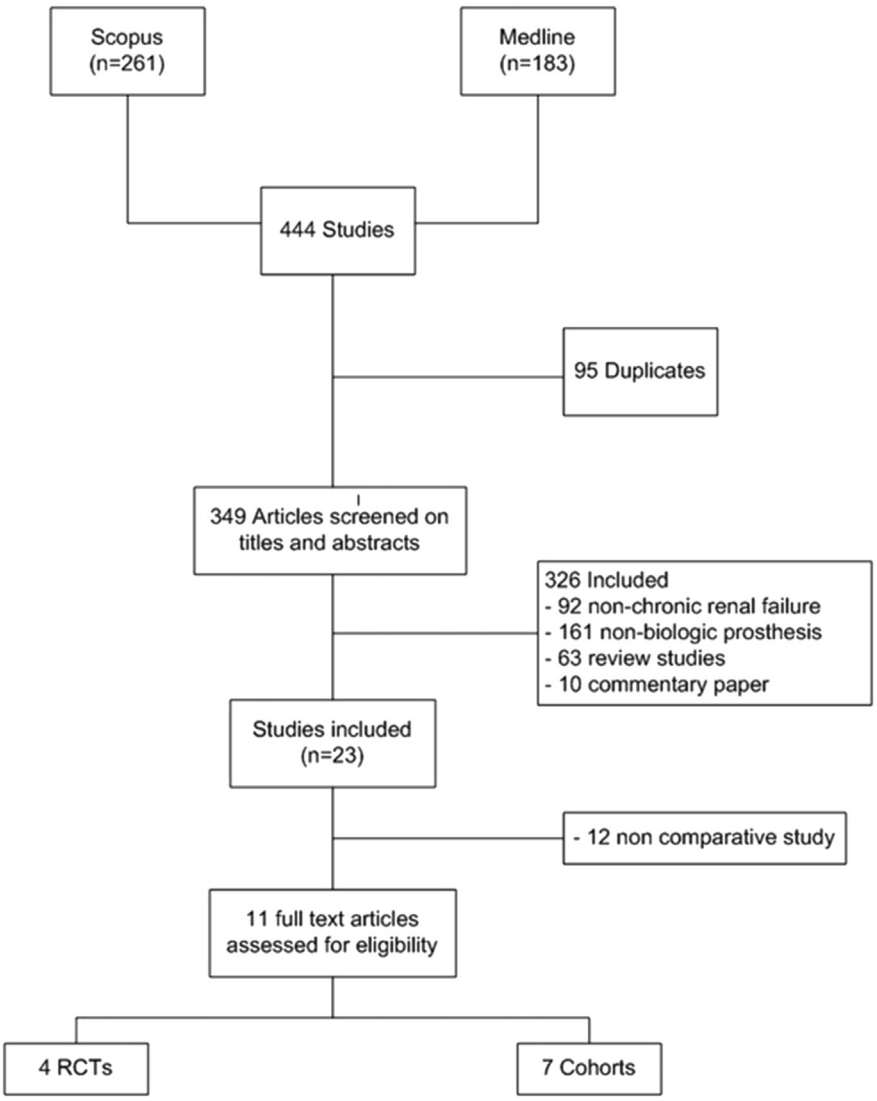

Fig. 1. Identification of studies for inclusion from PRISMA guideline.

a random effects model using the Der-Simonian and Laird method was applied for pooling RRs, otherwise the fixed effects model was used.

Meta-regression analysis was used to assess the source of heterogeneity by fitting age, and type of wound in the meta-regression model. Funnel plot with or without contour-enhancement was applied to detect publication bias due to small study effects. Egger's test was used for assessing the asymmetry of the funnel plot. All analyses were performed using STATA version 14.0. A P-value < 0.05 was considered statistically significant, except for the

Table 1
Characteristics of comparative studies that had biologic prosthesis.

Authors	Year	Study design	Number of patients	Procedure	Autologous veins graft	Biologic prosthesis	Polytetrafluoroethylene	Country
Eikhoff et al. [6]	1983	RCT	104	Femoro-popliteal bypass	NA[a]	50	54	Denmark
Eikhoff et al. [5]	1987	RCT	105	Femoro-popliteal bypass	NA[a]	50	55	Denmark
Mccollum et al. [11]	1991	RCT	191	Femoro-popliteal bypass	NA[a]	87	104	United Kingdom
Enzler et al. [7]	1996	Cohort	429	Hemodialysis access	301	59	69	Switzerland
Koch et al. [10]	1996	Cohort	347	Femoro-popliteal bypass	63	112	172	Germany
Wang et al. [14]	1996	Cohort	109	Hemodialysis access	NA[a]	61	48	Taiwan
Bacchini et al. [4]	2001	Cohort	911	Hemodialysis access	862	22	63	Italy
Glickman et al. [8]	2003	Cohort	74	Hemodialysis access	NA[a]	59	15	USA
Katzman et al. [9]	2005	Cohort	276	Hemodialysis access	NA[a]	183	93	USA
Morosetti et al. [12]	2011	RCT	57	Hemodialysis access	30	27	NA	Italy
Ozpak et al. [13]	2015	Cohort	24	Axillary bypass	NA[a]	12	12	Turkey

[a] NA = not applicable.

Table 2
Quality assessment of the included studies.

Cohort studies							
Authors (year)	Representative of studied subjects		Ascertainment of outcome		Ascertainment of intervention		Confounding bias
Enzler et al. (1996) [7]	yes		yes		yes		no
Koch et al. (1996) [10]	yes		yes		yes		no
Wang et al. (1996) [14]	yes		yes		yes		yes
Bacchini et al. (2001) [4]	yes		yes		yes		no
Glickman et al. (2003) [8]	no		yes		yes		yes
Katzman et al. (2005) [9]	no		yes		yes		yes
Ozpak et al. (2015) [13]	no		yes		yes		no
RCT study							
Authors (year)	Adequate sequence generation	Adequate allocation concealment	Blinding	Address incomplete outcome data	Selective outcome report	Free other bias	Description of other bias
Eikhoff et al. (1983) [6]	no	yes	no	no	yes	no	no
Eikhoff et al. (1987) [5]	yes	yes	no	no	yes	no	no
Mccollum et al. (1991) [11]	yes	yes	no	yes	yes	no	no
Morosetti et al. (2011) [12]	no	no	no	yes	yes	no	no

Yes = low risk of bias.

heterogeneity test for which $p < 0.1$ was used.

3. Results

3.1. Identifying studies

A flow diagram of the study selection process is shown in Fig. 1. The initial literature search identified 183 and 261 studies from PubMed and Scopus databases, respectively. Among these 444 studies, 95 studies were duplicates, leaving 349 studies for title or abstract review. After reviewing, 326 studies were ineligible leaving 23 studies for review full articles. Among 23, 12 studies were not comparative studies, leaving 11 studies with a total of 2627 patients available for extraction and analysis. Agreement for selection of studies and data extractions between the two reviewers were 92·2% ((kappa = 0.92, $p < 0.001$) and 93.9% (kappa = 0.93, $p < 0.001$) for outcomes. Characteristics of the 11 included studies are described in Table 1 [4–14]. Among them, 4 studies were

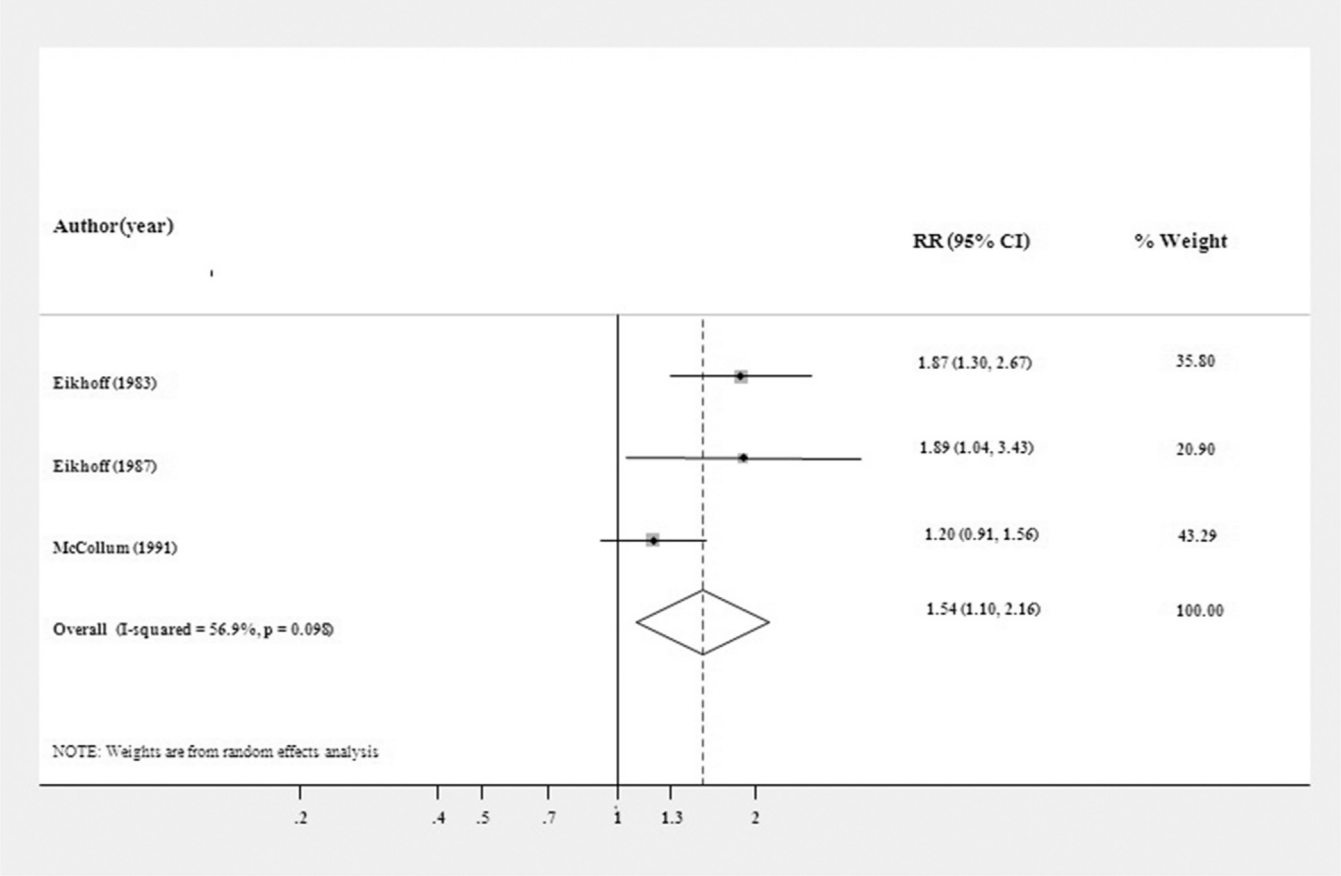

Fig. 2. Meta-analysis of graft patency between BP and PTFE.

randomized RCTs [5,6,11,12] whereas 7 studies were cohorts [4,7–10,13,14]. Most of the studies were from the European **countries**(7/11). Five studies used biologic prosthesis (human umbilical vein and bovine mesenteric vein) while 6 studies used biosynthetic prosthesis [4–14]. Seven studies compared BP with PTFE [4,7–10,13,14] and 3 studies compared PTFE with VG [4,7,10].

3.2. Risk of bias assessment

Among 7 cohorts [4,7–10,13,14], low risk of selection bias from the use of representative cases was found in 4 (57.14%) studies [4,7,10,14]. The ascertainment of all outcomes was clearly described in all studies [4,7–10,13,14]. The ascertainment of intervention was clear in all studies [4,7–10,13,14]. Confounding bias was found likely to be present in 4 (57.14%) studies [4,7,10,13].

In the RCT study, all studies [5,6,11,12] had low risk of bias in and selective outcome reports. However, in the domains of blinding and sequence generations, allocation concealments, and address incomplete outcome data 100%, 50%, 25%, and 50% of studies had high risk of bias, respectively. High risk of bias was found in the domains of free of other bias and description of other bias (Table 2).

3.3. Graft patency

Comparing biologic prosthesis (BP) VS PTFE, pooling was based on 3 RCTs with a sample size of 187 vs 213. The RR was moderately heterogeneous (Chi-square = 4.64 (d.f. = 2) p = 0.098; I^2 = 56.90%), see Fig. 2. Pooling with a random-effect model yielded the pooled RR of 1.54 (95% CI: 1.10, 2.16), indicating 54% higher graft patency in BP than PTFE). A sensitivity analysis was performed by adding the 7 cohorts in this pooling which yield similar results with the pooled RR of 1.29 (95% CI: 1.15, 1.45) (Fig. 3). Neither Egger's test nor the funnel plot suggested asymmetry (coefficient = 1.44, SE = 0.64, p = 0.05).

Comparing biologic prosthesis (BP) VS autogenous veins graft (VG), the pooled RR of graft patency for BP vs VG was 0.74 (95% CI, 0.55, 1.00) (Fig. 4), indicating 26% lower graft patency but not significant in BP than VG. Neither Egger's test nor the funnel plot suggested asymmetry (coefficient = 1.11, SE = 1.34, p = 0.56).

4. Discussion

The use of vascular prosthesis is unavoidable in a significant number of patients who need vascular conduit or access for hemodialysis. The ideal prosthetic material for vascular construction with unsuitable superficial vein network remains a matter for debate, as there have been no large prospective, randomized trials; moreover, the materials have been used under different circumstances and the methods for reporting patency have not been uniform [16]. Our first meta-analysis indicated that the

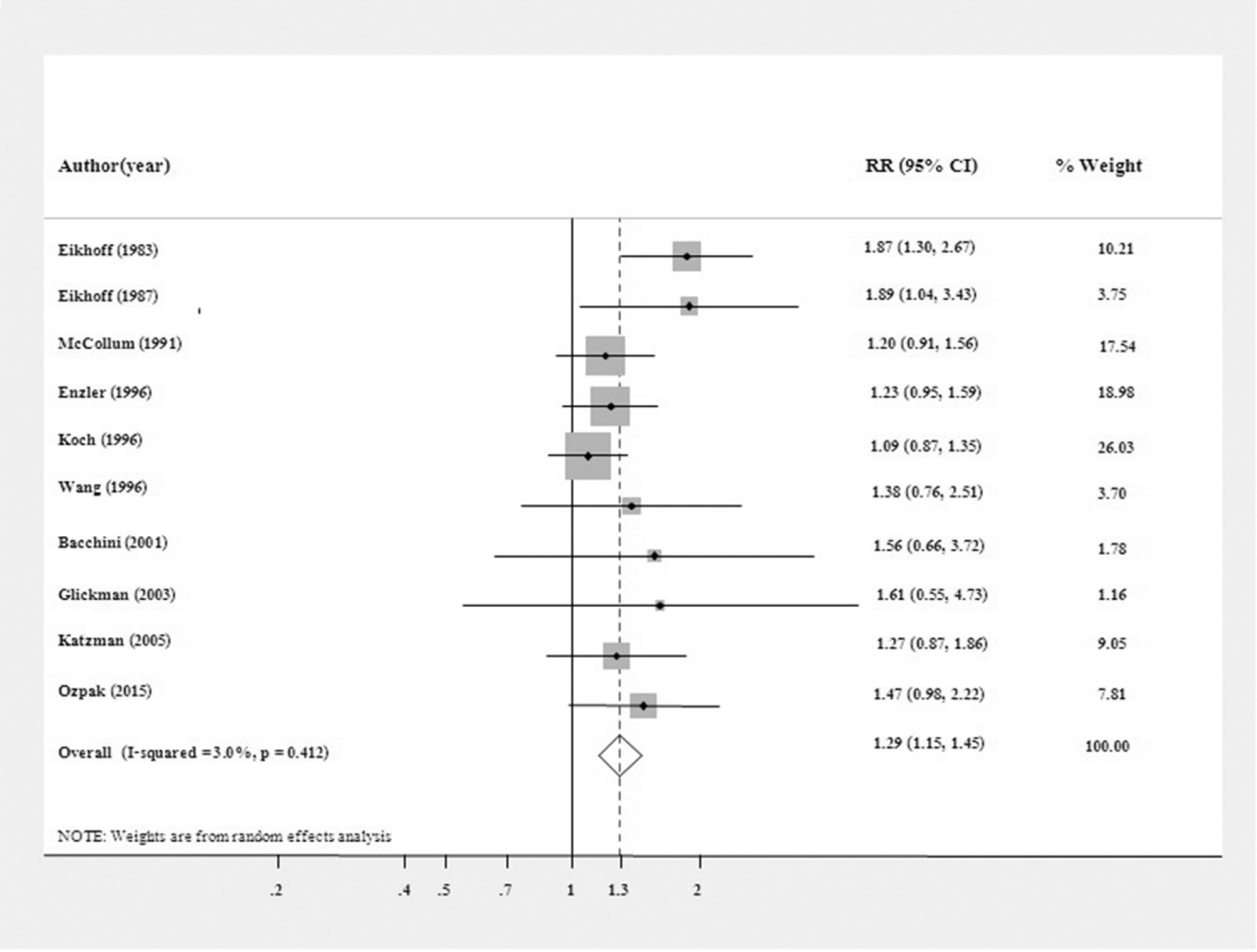

Fig. 3. Sensitivity analysis of graft patency between BP and PTFE.

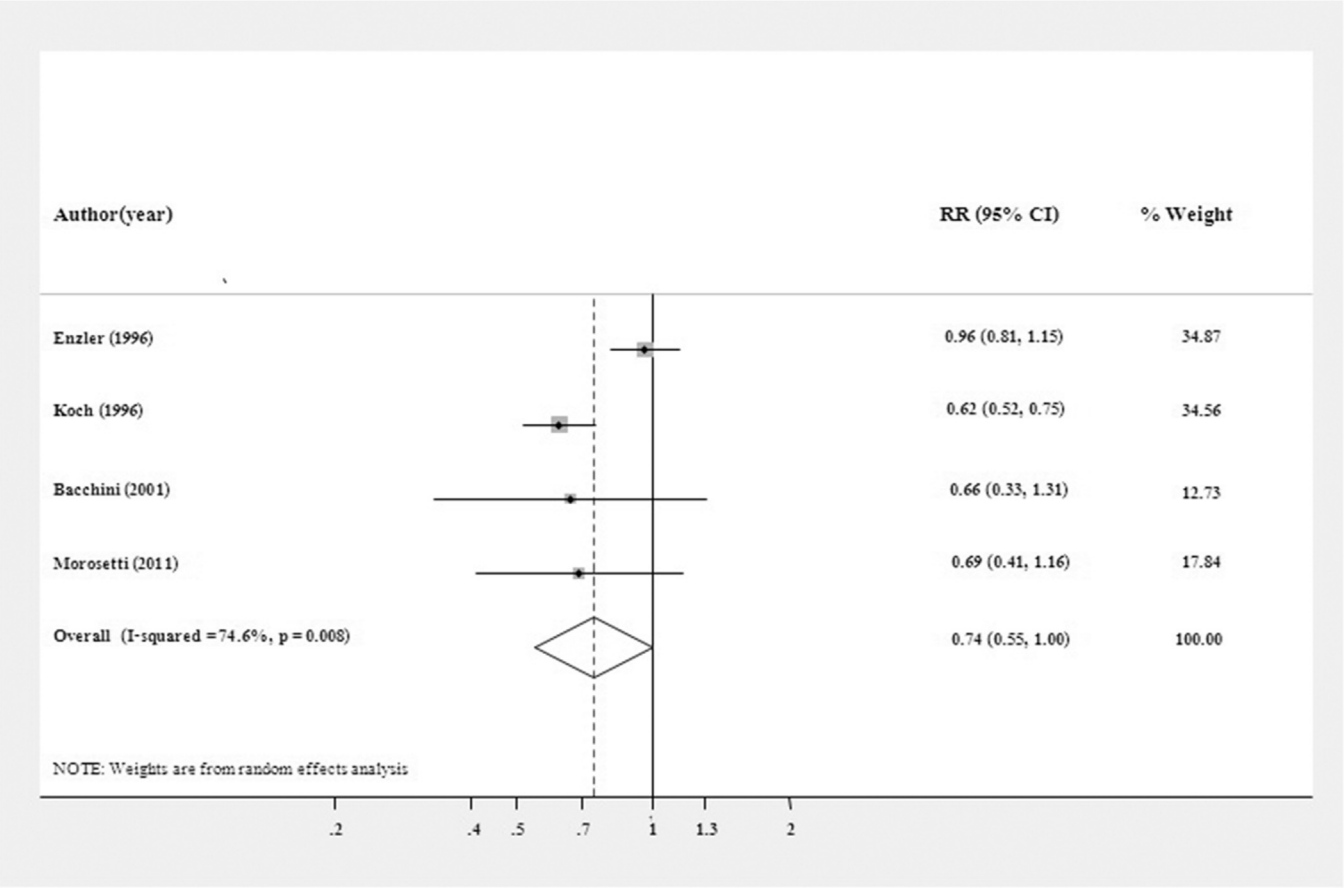

Fig. 4. Meta-analysis all study of graft patency between BP and VG.

biosynthetic prosthesis might be benefit over PTFE by increasing graft patency. Comparing biologic prosthesis (BP) and autogenous veins graft (VG) found that graft patency for BP was 26% lower than VG but not statistically significance.

A number of alternative graft materials are commercial available. The bioprosthesis derived from bovine mesenteric veins, obtained by process of glutaraldehyde cross linking, has been reported longer patency, lower rates of reoperation, and lower incidence of thrombosis [17]. Biosynthetic prosthesis, a glutaraldehyde-tanned ovine collagen-polyester composite, obtained by inserting polyester mesh-covered mandrills beneath the cutaneous trunci muscle of sheep has the advantage of the natural collagen, deprived of its immunogenicity and the polyester net provides increased mechanical resistance to deterioration [18]. Polytetrafluoroethylene (PTFE) is the most popular graft material, despite its higher incidence of graft thrombosis, infection, and seroma formation. Multiple reports have shown PTFE graft to be adequate alternative conduit for vascular reconstruction. Heparin-bonded prosthetic graft which are now widely using with significant results available in literature is an alternative to biologic prosthesis. Systemic review and meta-analysis should be done in this topic.

The strength of our studies is that we analyzed the RCTs that could minimize selection and confounding biases between BP and PTFE. A sensitivity analysis was performed by including comparative cohort studies to confirm the results. However, our results were pooled based on moderate heterogeneity across included studies. The number of included RCTs was also quite small. Additional data can not accessed (other journals e.g. EMBASE, unpublished data). The question asked in this meta-analysis is unable to compare all three grafts, but compares biosynthetic and PTFE and biosynthetic and PTFE and VG in two separate statistical tests. Furthermore, some studies (25–50%) had high risk of bias in sequence generations, allocation concealments, and address incomplete outcome data. Therefore, further large scale RCTs or updated meta-analysis is required to confirm our results.

5. Conclusion

Biosynthetic vascular prostheses are promising alternative graft material when an autologous vein is limited, both for the hemodialysis assess and femoropopliteal bypass. An updated meta-analysis or a large scale randomized control trial is required to confirm this results.

Ethical approval

No ethic approval.

Sources of funding

No funding.

Author contribution

Chumpon Wilasrusmee: study design, data collections, data analysis, writing.

Boonying Siribumrungwong: data collections.

Suthas Horsirimanont: data collections.
Napaphat Poprom: data analysis.
Jakrapan Jirasiritham: data collections.
Ammarin Thakkinstian: study design, data collections, data analysis, writing.

Conflicts of interest

No conflicts of interest.

Guarantor

Professor Wachira Kochakarn, Dean of Department of Surgery, Faculty of Medicine, Ramathibodi Hospital, Mahidol University.

Appendix 1

Search strategy for PubMed and Scopus

1. Chronic renal failure
2. Peripheral arterial disease
3. Arterial stenosis
4. Arterial occlusion
5. Vascular access
6. Femoropopliteal bypass
7. Hemodialysis
8. Biologic prosthesis
9. Polytetrafluoroethylene
10. Prosthesis
11. Autologous veins graft
12. Graft patency
13. Graft survival
14. Graft thrombosis
15. Graft infection
16. Graft dysfunction
17. (1 or 2 or 3 or 4 or 5 or 6 or 7)
18. (8 or 9 or 10 or 11)
19. (12 or 13 or 14 or 15 or 16)
20. (17 or 19)
21. (18 and 20)

Appendix 2. Risk of bias assessment form

For Cohort study

Author	Domain	Item	Low risk of bias
	Selection bias	Representative of cohorts A. Consecutive/randomly selected from cases population with extensive inclusion criteria B. Spectrum of diseases C. Did not mention	
	Information bias	Ascertainment of outcome measurement A. Cleary describe definition of outcomes B. Did not describe Ascertainment of Interventions A. No switching of treatment between groups B. Not describe	
	Confounding bias	Confounding bias A. Adjusting confounding factors in analysis B. Did not adjust confounding factors	

For RCT study

Author	Adequate sequence generation	Adequate allocation concealment	Blinding	Address incomplete outcome data	Selective outcome report	Free other bias	Description of other bias

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