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Reviewer A

1. Title: I don't think it is appropriate to use abbreviations of the different type of balloons in the title itself.

Response: Thank you for the suggestion. We have modified the title of our manuscript to: “Comparative efficacy of five balloons for treating autogenous arteriovenous fistula stenosis: a Bayesian network meta-analysis (Page 1, Line 1-2).

2. Introduction - please use the updated KDOQI guidelines from LOK and not the older version. There are currently no head-to-head studies between different named balloons please correct intro.

Response: Thank you for the suggestion. Firstly, we consulted the PubMed database, however, we found that the literature cited in our manuscript is already up-to-date. If you find any updated documents, please do not hesitate to comment. We are willing to correct our manuscripts at any time. Secondly, the sentences about “head-to head studies” in the introduction section was indeed inappropriate and we have removed it.

3. There needs to be some explanation of the difference in the types of balloons being examined and what the differences between for example DEB vs DCB and HPB vs POBA. Cutting balloons were included so why do people use them? how come no scoring balloons then?

Response: Thank you for the suggestion. We added some explanation of the differences between these balloons in the manuscript. “Therefore, several new types of balloons have been proposed and tested. High-pressure balloon (HPB), whose burst pressure is more than 14 atm, may be better for resistant lesions than PBA [1]. An alternative to HPB is a cutting balloon (CtB). The application of CtB in treating resistant stenosis was first described in 1995 in a case report [2]. Three or four cutting blades were incorporated into the CtB. It could cut and disrupt the fibroelastic continuity of the ring of neointimal hyperplasia. A drug-coated balloon (DCB) and a drug-eluting balloon (DEB) are also common balloons; both of them have a drug coating. However, the manufacturing processes may not be identical, leading to differences in effectiveness. In general, direct evidence on different balloons is rare.” (Page 3 Line 46-55)

Regarding the scoring balloon, although it has been used in the treatment of peripheral vascular disease. However, the use of scoring balloon for the treatment of

AVF stenosis has been rarely reported [3,4]. And the number of patients involved in these studies is limited. Moreover, there were no randomized controlled studies currently. Therefore, scoring balloon is not mentioned in our study.

[1] Maglione J, Bergersen L, Lock JE, et al. Ultra-high-pressure balloon angioplasty for treatment of resistant stenoses within or adjacent to previously implanted pulmonary arterial stents. *Circ Cardiovasc Interv.* 2009;2(1):52-58.

[2] Vorwerk D, Günther RW, Schürmann K, Sieberth HG. Use of a cutting balloon for dilatation of a resistant venous stenosis of a hemodialysis fistula. *Cardiovasc Intervent Radiol.* 1995;18(1):62-64.

[3] Ross JR. Restoring arteriovenous access: Pilot study using a scoring balloon in 50 patients. *J Vasc Access.* 2021;22(4):623-628.

[4] Sato R, Sato T, Shirasawa Y, et al. A case series of favorable vessel dilatation using a nitinol scoring element-equipped helical balloon catheter (AngioSculpt®). *J Vasc Access.* 2019;20(1-suppl):93-96.

4. You excluded recurrent lesions? But a lot of these studies included recurrent lesions so how could you tell that all the lesions were first time in nature?

Response: Thank you for the suggestion. In the inclusion criteria, we referred to “restenosis of AVF was excluded ...”. However, this is inconsistent with the study we actually performed. So we removed it. Among the studies included in our study, there were indeed some studies that investigated “stenosis” and “restenosis” together. In order to make the analysis as comprehensive as possible, we still analyzed them. This may indeed create inaccuracies in the conclusions, whereupon we added the following sentences in limitation section “Finally, the patient inclusion criteria of different RCTs were not completely consistent. Therefore, an RCT performed by our center may be needed to analyze different balloons comprehensively.” (Page 11 Line 234-237)

5. Should there not be a breakdown of the benefit of each balloon for different parts of the AVF circuit e.g. JAS vs non JAS lesions and outflow vein vs cannulation zones?

Response: Thank you for the comments. Although most of studies collected the data about the location of AVF stenosis e.g. (perianastomotic and outflow venous). Meanwhile, many studies also collected the data about effectiveness (primary patency of AVF) of different balloons. Unfortunately, none of these studies counted the primary patency rates of AVF circuit separately by stenosis location. Therefore, we failed to investigate this outcome in our study because of the characteristics of meta-analysis. We will certainly update our findings in a timely manner if such data become available in the future.

6. Were scented circuits included?

Response: Thank you for the comments. Most of the studies included in our meta-analysis collected the data about the location of AVF stenosis. And some studies included AVF circuit. However, as in the response to previous comment, only a few studies analysis the patency rate of AVF circuit. The data they involved was too rare to be analyzed. If more data could be acquired in the future, we will update our results in a timely manner timely as well.

7. I find the statistics section hard to follow for a non-mathematician and I think you should rephrase or rewrite this section for readers who are not bent this way.

Response: Thank you for the suggestions. We have modified this section as requested. Meanwhile, the following sentences were added in our manuscript "... Second, the NMA methodology allows the comparison of any two treatments within the network even a direct comparison from a trial is not available. Therefore, NMA was performed to compare different treatments. The models were fit using GeMTC software. ORs <1 or >1 favored one of the compared treatments over the other, whereas ORs equal to 1 indicated equivalent patency rates. Briefly, statistical significance was indicated by the exclusion of 1 from 95% CIs.

The probability values of each treatment were summarized as the surface under the cumulative ranking curve (SUCRA) (0%~100%), with larger surface under the curve denoting more effective treatments..." (Page 5-6 Line 107-115)

8. You need to define what you mean by clinical effectiveness.

Response: Thank you for the suggestion. And it is very useful. "Clinical effectiveness" refers to "patency rates" mentioned above. So we replaced "clinical effectiveness" with "patency rates" in manuscript. (Page 12 Line 243)

9. Summary - too strong how do you conclude long term results when you have gone out to one year only? we see with most DCBs/DEBs that the TLPP drops between the 6-12 months interval...

Response: Thank you for the comment. We reviewed the literatures included in our study carefully. We found that 1-year patency rates of AVFs ranged from 11.1% to 55.8%. Therefore, the authors hold that one year may be a relatively long follow-up time for stenotic AVFs treated with different balloons. So we think that the results of one year could be considered as "long term results" for these AVFs. Moreover, we also refer to other meta-analyses. Postoperative follow-up period mentioned in their manuscript is also 12 months [5]. Meanwhile, another study [6] also suggested that there are few RCT studies with a follow-up period of more than 12 months (Figure 1).

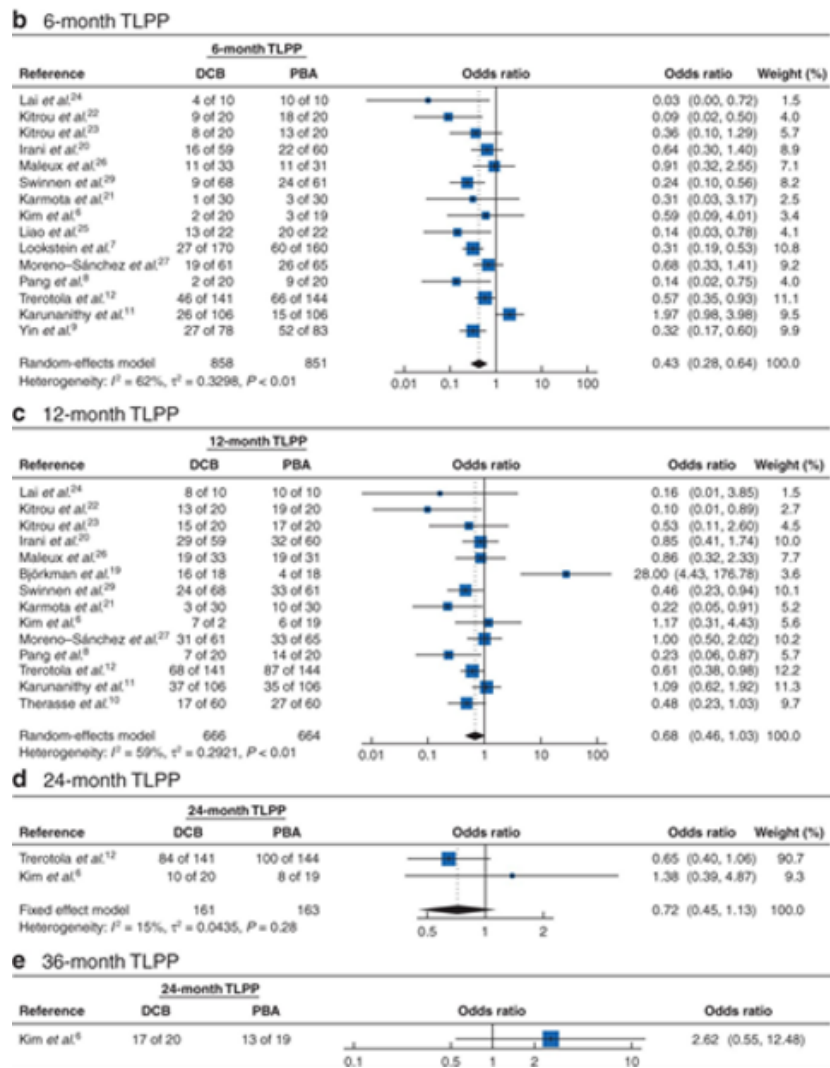


Figure 1

[5] Liu C, Wolfers M, Awan BZ, et al. Drug-Coated Balloon Versus Plain Balloon Angioplasty for Hemodialysis Dysfunction: A Meta-Analysis of Randomized Controlled Trials. *J Am Heart Assoc.* 2021;10(23):e022060.

[6] Hu H, Tan Q, Wang J, Liu Y, Yang Y, Zhao J. Drug-coated balloon angioplasty for failing haemodialysis access: meta-analysis of randomized clinical trials. *Br J Surg.* 2021;108(11):1293-1303.

10. How do the authors differentiate between calcified and resistant lesions compared to compliant lesions?

Response: Thank you very much for the comments. Actually, vascular calcification is one of the causes of resistant lesion formation. Resistant lesions did not entirely result from vascular calcification. Resistant lesions may also be caused by other reasons, such as fibroproliferation of blood vessels. The reason why we mention calcified and resistant lesions is simply because we would like to briefly recount the advantages of

HPB. Therefore, we modified our manuscript as follow “However, HPB had its unique advantages as well. A retrospective study suggested that the efficacy of HPB for resistant lesions might be better than that of PBA [7]. Meanwhile, its cost might be less than CtB [8].” (Page 9-10 Line 197-199) Meanwhile, we removed the “calcified” in the final sentence. (Page 12 Line 245)

[7] Wu CC, Lin MC, Pu SY, et al. Comparison of cutting balloon versus high-pressure balloon angioplasty for resistant venous stenoses of native hemodialysis fistulas. *J Vasc Interv Radiol.* 2008;19(6):877-883.

[8] Trerotola SO, Stavropoulos SW, Shlansky-Goldberg R, Tuite CM, Kobrin S, Rudnick MR. Hemodialysis-related venous stenosis: treatment with ultrahigh-pressure angioplasty balloons. *Radiology.* 2004;231(1):259-262.

11. Any cost-effectiveness data available?

Response: Thank you very much for your comments. We do expect the data about the costs of these patients. Unfortunately, no study provided the data about the costs of different balloons. All studies included in our meta-analysis mainly focused on the effectiveness (patency rate, complications, etc.) of different balloons. Therefore, we added following sentences in the limitation section “Moreover, we could not obtain relevant data about the costs of different balloons. Future studies should consider both cost and efficacy.” (Page 11 Line233-234)

Reviewer B

Abstract:

Abbreviations need to be explained upon first use: PBA, HPB, AVF.

Response: Thank you for the suggestion. It is true that the full names of the words above should be used in the title. However, it may cause the title to be excessively long. Therefore, we modified the title of our manuscript to: “Comparative efficacy of five balloons for treating autogenous arteriovenous fistula stenosis: a Bayesian network meta-analysis”. (Page 1, Line 1-2)

Conclusion:

Need to expand the sentence. “effective treatment” in maintaining patency rate in a year?

Response: Thank you for the suggestion. “Effective treatment” is indeed too simple. Therefore, we tried our best to explain this part in detail. Therefore, we modified our manuscript as follow “DEB may be the most effective treatment of AVF stenosis,

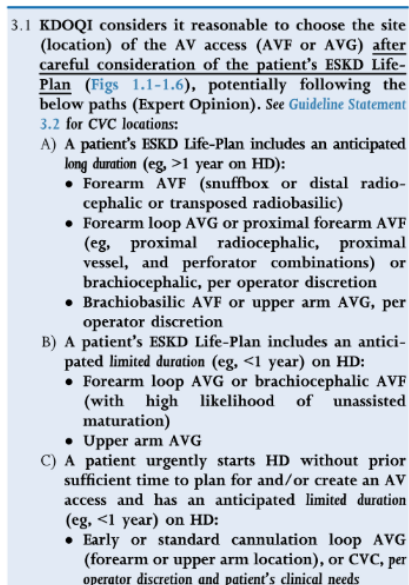
followed by DCB. However, prospective studies involving large sample sizes of clinical trials and a direct comparison between DEB and DCB are required to clarify the individual value of different treatment options.” (Page 2 Line 24-27)

Introduction:

Page 2 line 58: “mostly the radial artery and cephalic vein”. Citation please.

Response: Thank you for the suggestion. We have added references as requested. And we modified this sentence as follow “Meanwhile, radiocephalic AVF may be the first choice [9]”. (Page 2 Line 40). As shown in figure 2 and 3.

[9] Lok CE, Huber TS, Lee T, et al. KDOQI Clinical Practice Guideline for Vascular Access: 2019 Update. Am J Kidney Dis. 2020;75(4 Suppl 2): S1-S164.



3.1 KDOQI considers it reasonable to choose the site (location) of the AV access (AVF or AVG) after careful consideration of the patient's ESKD Life-Plan (Figs 1.1-1.6), potentially following the below paths (Expert Opinion). See [Guideline Statement 3.2](#) for CVC locations:

A) A patient's ESKD Life-Plan includes an anticipated long duration (eg, >1 year on HD):

- Forearm AVF (snuffbox or distal radiocephalic or transposed radiobasilic)
- Forearm loop AVG or proximal forearm AVF (eg, proximal radiocephalic, proximal vessel, and perforator combinations) or brachiocephalic, per operator discretion
- Brachiobasilic AVF or upper arm AVG, per operator discretion

B) A patient's ESKD Life-Plan includes an anticipated limited duration (eg, <1 year) on HD:

- Forearm loop AVG or brachiocephalic AVF (with high likelihood of unassisted maturation)
- Upper arm AVG

C) A patient urgently starts HD without prior sufficient time to plan for and/or create an AV access and has an anticipated limited duration (eg, <1 year) on HD:

- Early or standard cannulation loop AVG (forearm or upper arm location), or CVC, per operator discretion and patient's clinical needs

Figure 2

Line 67: “Previously, original data on the effect of these treatment strategies were reported from several randomized controlled trials (RCTs). Nevertheless, direct evidence from interventions evaluated directly in head-to-head trials is rare.” There’s redundancy in this sentence. Also, citation is needed.

Response: Thank you for the suggestion. There are indeed some redundancies in this sentence after repeated consideration. Therefore, we removed part of it and rephrased rest sentences as follow “In general, direct evidence on different balloons is rare. Therefore, which new type of balloons can provide better outcomes still remains unclear.” (Page 3, Line 55-56)

Line 78: “The findings of this study were critical as they offer a clinical summary that can guide treatment decision.” This sentence can be deleted.

Response: Thank you for the suggestion. We have deleted it as requested.

Methods:

Line 90: “Two investigators (XXX and XXX)”. Who are XXX? XXX is used multiple times in this section.

Response: Thank you for the suggestion. Due to the publication policy, we have used “XXX” instead of true name of the authors. Two authors who reviewed the references and judged the risk of bias were Yu Li (first author) and Wenhao Cui (second author). Meanwhile, the “third investigator” was Tao Luo (corresponding author). We have replaced all “XXX” in the manuscript with the true names of the authors. (Page 4 Line 73, 75 Page 5 Line 96)

Evaluation of publication bias is needed.

Response: Thank you for the suggestion. And publication bias is very useful. We checked the publication bias of our meta-analysis. Meanwhile, we added the following sentences in method section “Finally, potential publication bias was estimated using a funnel plot. A roughly symmetrical funnel plot indicated insignificant publication bias.” (Page 6 Line 123-124). Meanwhile, we added the following sentences in result section “A funnel plot representing the publication bias of the studies is presented in Figure 5. The funnel plot was symmetrical, indicating a slight publication bias.” (Page 7 Line 151-153)

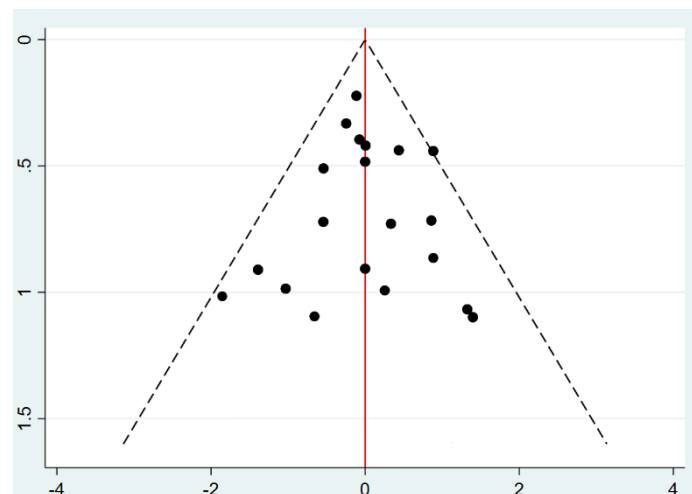


Figure 5 Funnel plot of selected studies

One concern regarding drug coated balloon is its reported higher mortality rate. I recommend investigating this outcome as well.

Response: Thank you for the suggestions. We did want to analyze the difference in

mortality. However, we reviewed the literatures which were included again and found that only three studies included in our meta-analysis analyzed the results of mortality outcome [10,11,12]. Meanwhile, the results from the studies showed that there was no significant difference in mortality between different groups. Moreover, the results from other meta-analysis also suggested that there was no difference in mortality between DCB and PBA groups [13,14]. Therefore, we think that we may be able to analyze the results of mortality again in the future. The data are now rare and not yet suitable for analysis.

[10] Lookstein RA, Haruguchi H, Ouriel K, et al. Drug-Coated Balloons for Dysfunctional Dialysis Arteriovenous Fistulas. *N Engl J Med*. 2020;383(8):733-742.

[11] Trerotola SO, Saad TF, Roy-Chaudhury P; Lutonix AV Clinical Trial Investigators. The Lutonix AV Randomized Trial of Paclitaxel-Coated Balloons in Arteriovenous Fistula Stenosis: 2-Year Results and Subgroup Analysis. *J Vasc Interv Radiol*. 2020;31(1):1-14. e5.

[12] Moreno-Sánchez T, Moreno-Ramírez M, Machancoses FH, et al. Efficacy of Paclitaxel Balloon for Hemodialysis Stenosis Fistulae After One Year Compared to High-Pressure Balloons: A Controlled, Multicenter, Randomized Trial. *Cardiovasc Intervent Radiol*. 2020;43(3):382-390.

[13] Liu C, Wolfers M, Awan BZ, et al. Drug-Coated Balloon Versus Plain Balloon Angioplasty for Hemodialysis Dysfunction: A Meta-Analysis of Randomized Controlled Trials. *J Am Heart Assoc*. 2021;10(23):e022060.

[14] Hu H, Tan Q, Wang J, et al. Drug-coated balloon angioplasty for failing haemodialysis access: meta-analysis of randomized clinical trials. *Br J Surg*. 2021;108(11):1293-1303.

RESULTS:

Please include p-values for all ORs.

Response: Thank you for the reminder. We have added all the p-values for the ORs of “Direct Meta-Analysis”. However, because of the characteristics of network meta-analysis. P-values will not be represented in the indirect meta-analysis (“Network Meta-Analysis”) and the following “Rank Probabilities”. And we also added the following sentences in Discussion section “The results of direct meta-analyses revealed that new types of balloons might not be superior to PBA in terms of primary patency after 3, 6, and 9 months. Moreover, the primary patency rate of new balloons after 12 months was significantly better than of PBA.” (Page 9 Line 181-184). And these sentences were aimed to discuss the results of direct meta-analyses briefly.

Is there evaluation of outcomes beyond 12-months?

Response: Thank you for the comment. After carefully reading the literatures included in our meta-analysis, we found only five studies listed the data about the patency rates over 12 months [15-19]. However, only few data could be extracted from them. Therefore, no reliable conclusion could be drawn. Moreover, some study showed that there was little differences regard of data beyond 12 months (Figure 3). This is also consistent with the experience of our center. Therefore, there is no evaluation of outcomes beyond 12 months.

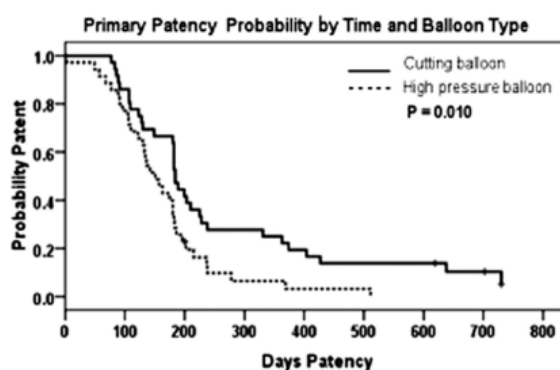


Figure 2. Kaplan-Meier analysis comparing the primary target lesion patency of CBA versus HPBA. The primary target lesion patency for CBA was significantly ($P = .010$) superior to that of HPBA (HR, 1.895; 95% CI, 1.148-3.126).

Figure 3

[15] Lučev J, Breznik S, Dinevski D, et al. Endovascular Treatment of Haemodialysis Arteriovenous Fistula with Drug-Coated Balloon Angioplasty: A Single-Centre Study. *Cardiovasc Intervent Radiol*. 2018;41(6):882-889.

[16] Trerotola SO, Saad TF, Roy-Chaudhury P; Lutonix AV Clinical Trial Investigators. The Lutonix AV Randomized Trial of Paclitaxel-Coated Balloons in Arteriovenous Fistula Stenosis: 2-Year Results and Subgroup Analysis. *J Vasc Interv Radiol*. 2020;31(1):1-14. e5.

[17] Kariya S, Tanigawa N, Kojima H, et al. Primary patency with cutting and conventional balloon angioplasty for different types of hemodialysis access stenosis. *Radiology*. 2007;243(2):578-587.

[18] Saleh HM, Gabr AK, Tawfik MM, et al. Prospective, randomized study of cutting balloon angioplasty versus conventional balloon angioplasty for the treatment of hemodialysis access stenoses. *J Vasc Surg*. 2014;60(3):735-740.

[19] Aftab SA, Tay KH, Irani FG, et al. Randomized clinical trial of cutting balloon angioplasty versus high-pressure balloon angioplasty in hemodialysis arteriovenous fistula stenoses resistant to conventional balloon angioplasty. *J Vasc Interv Radiol*. 2014;25(2):190-198.

Definition of primary patency varies among studies. I recommend creating a table addressing the definition of primary patency in each study.

Response: Thank you for the comments. We reviewed the studies included in our meta-analysis once again and we found that almost all studies highlighted the definition of technical success of PTA procedure “less than 30% residual stenosis and the ability to perform at least one successful dialysis”. Meanwhile, most of the studies reported the intervention criteria of PTA procedure after vascular anastomosis. However, among the numerous indicators, core indicators can be summarized as follow: (a) Angiographically confirmed stenosis greater than 50%, (b) decrease of blood flow in AVF by more than 20%, (c) obvious clinical symptoms and inability to perform normal dialysis. We can be sure that all the studies which reported primary patency rates followed the criteria. Therefore, in the author's opinion, the definition of primary patency of different study can be considered roughly the same. So it may not be necessary to add a column to Table 1. However, we found that the data about “type of AVF” may important in our study, so we added the data in Table 1.

Please include a table listing the types of AVF and their percentage. This information can serve as a valuable reference.

Response: Thank you for the comments. This information is really meaningful data. Therefore, we tried our best to collect the data about the types of AVF and their number. And we also added them into table 1. (Table 1)

Page 5 Line 194: “ranked best”. Please us an alternative such as “xxx is superior than xxx”.

Response: Thank you for the suggestion. We have modified the sentence as request and rewrote them as follow “DCB was superior to other balloons in terms of the patency rate after 3 months. Consistent with the result after 3 months, DEB was superior to other balloons after 6, 9, and 12 months.” (Page 8 Line 168-170)

DISCUSSION:

There are several meta-analyses published recently comparing difference treatment modalities. Please include and discuss these articles:

Liu C, Wolfers M, Awan BE, Ali I, Lorenzana AM, Smith Q, Tadros G, Yu Q. Drug-Coated Balloon Versus Plain Balloon Angioplasty for Hemodialysis Dysfunction: A Meta-Analysis of Randomized Controlled Trials. Journal of the American Heart Association. 2021 Dec 7;10(23):e022060.

Hu H, Tan Q, Wang J, Liu Y, Yang Y, Zhao J. Drug-coated balloon angioplasty for failing haemodialysis access: meta-analysis of randomized clinical trials. British Journal of Surgery. 2021 Nov;108(11):1293-303.

Response: Thank you for the reminder. Because our research was carried out earlier, we failed to include these two articles. We have cited these articles in suitable location and discussed the results of them briefly. We added the following sentences in our manuscript “The results demonstrated that both DEB and DCB had a statistically higher patency rate compared with PBA at all time points, which was consistent with the results of several recently published studies [20,21]. Meanwhile, both these studies demonstrated that the use of DCB did not cause a significant increase in patient mortality, indicating the high safety of DCB compared with PBA.” (Page 10 Line 210-215)

[20] Liu C, Wolfers M, Awan BZ, et al. Drug-Coated Balloon Versus Plain Balloon Angioplasty for Hemodialysis Dysfunction: A Meta-Analysis of Randomized Controlled Trials. *J Am Heart Assoc.* 2021;10(23):e022060.

[21] Hu H, Tan Q, Wang J, et al. Drug-coated balloon angioplasty for failing haemodialysis access: meta-analysis of randomized clinical trials. *Br J Surg.* 2021;108(11):1293-1303.

Page 5 Line 207: “In our study, results of the NMA revealed that short-term (3 and 6 months) treatment outcomes of HPB were better than that of PBA, but the outcomes of 9 and 12 months were contrary”. Results beyond 6 months are underpowered.

Response: Thank you for the suggestion. The results beyond 6 months were indeed underpower. However, our previous study which published in 2021 reached a similar conclusion. To testify the results of the present study, we also cite it. And we have modified the sentences as follow “However, our study failed to demonstrate that the long-term (9 and 12 months) outcomes of HPB were also better than those of PBA. Similar conclusions could also be drawn from our previous study [22]” (Page 9 Line 186-188)

[22] Li Y, Cui W, Wang J, et al. Efficacy of High-Pressure Balloon for the Treatment of Arteriovenous Fistula Stenosis: A Meta-Analysis [published online ahead of print, 2021 Dec 2]. *J Endovasc Ther.* 2021;15266028211058690.

Page 6 Line 239: “The drug coating of DEB contains special materials that control the release rate of the drug to obtain a durable effect”. Please elaborate on “special materials”.

Response: Thank you for the suggestion. More exactly, the materials applied in the new balloons were similar with the old one. However, the processing technology may different. Therefore, we modified the sentences as follow “A study performed by Buszman et al. also demonstrated that the new-generation balloons could result in

homogeneous and circumferential coatings, which was caused by a proprietary dipping process applied in these balloons. It led to the preferential deposition of the paclitaxel–iopromide formulation in the folds of the balloon [23].” (Page 11 Line 222-226)

[23] Buszman PP, Tellez A, Afari ME, et al. Tissue uptake, distribution, and healing response after delivery of paclitaxel via second-generation iopromide-based balloon coating: a comparison with the first-generation technology in the iliofemoral porcine model. *JACC Cardiovasc Interv.* 2013;6(8):883-890.

I highly recommend authors have a native speaker revise the wording of this article. In many occasions, the wordings are not scientific and/or confusing to comprehend.

Response: Thank you for the suggestion. We performed a native speaker revising again as requested. And the certification has been attached as well.

Reviewer C

Nice analysis to help physicians dealing with recurrent AVF stenosis improve and prolong the effectiveness of treatment. This is an area of intervention where the options are plenty but the results are not consistently long lasting. There is no consensus on what is the best treatment option for these patients and hence this analysis is very timely and hopefully provide physicians dealing with this issue some clarity.

Response: Thank you for the comments. We hope our study could provide a new perspective for vascular surgeons and nephrologists in the future as well.