PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Covered Stents Versus Balloon Angioplasty for Failure of Arteriovenous Access: A Systematic Review and Meta-Analysis
AUTHORS	Ng, Benjamin; Fugger, Magnus; Onakpoya, Igho; Macdonald, Andrew; Heneghan, Carl

VERSION 1 – REVIEW

REVIEWER	Kennedy, Sean McMaster University
REVIEW RETURNED	31-Oct-2020

GENERAL COMMENTS	Well done and interesting meta-analysis. Adheres to appropriate guidelines on meta-analysis technique. Results and their limitations are well presented. A few issues should be addressed: A) Authors state: “Finally, we are aware of the potential of drug-eluting or drug-coated devices (stents or balloons) in dysfunctional AV access. A recent systematic review and metanalysis did not favour significant patency benefit of drug-coated balloon versus normal angioplasty (21). However, more research is needed to compare these drug eluting or drug-coated devices against covered stents.” This references a single meta-analysis which did not support the use of drug eluting technology in dialysis circuits. There have been several meta-analyses on this topic (JVIR Kennedy et al 2019, J Vasc Surg Wee et al. 2019) both of which supported drug eluting balloon technology. The authors selectively referenced one meta-analysis coming to one conclusion. Meanwhile, the meta-analysis they referenced themselves states they may have overestimated event rates (artificially worsening outcomes for drug eluting balloons) : “The derived number of events might then overestimate the true number. …This approach represents a more conservative attitude on the evaluation of a new device.” (PLOS One 2020 Liao et al.) Bottom line; for the authors of the present meta-analysis, it would be more appropriate to state that current meta-analysis results on this topic are conflicting and reference multiple recent meta-analyses aforementioned, rather than to selectively reference one not supporting the use of drug-coated balloons. Disclosure: I am the first author of Kennedy et al 2019 JVIR. B) Complications should be reported in results for each arm of each trial.

	C) Additional data on patient/treatment characteristics should be presented for each trial. Specifically, proportion of location of intervention (perianastomotic etc), number of prior interventions in these grafts/fistulas, graft/fistula characteristics (type of fistula, loop/straight graft proportions, etc) how patency was assessed at each time point in each study. D) Why is there only mention of AveNEW trial but not of AveVa trial? This should at least be mentioned as ongoing trial. https://clinicaltrials.gov/ct2/show/results/NCT02790606 E) Technical success is defined by the authors as "<30% residual stenosis after intervention". You go on to state in limitations "Secondly, the heterogeneity and technical definitions and protocols used by different studies may have impeded extraction and analysis of the data." Is this technical success definition consistent throughout all trials? Please clarify. F) Stent brands should be broken down per trial. G) "That almost all but one study focused on AV grafts limits the applicability of our pooled analysis to this patient population." Poorly worded rephrase. H) Generally, statements of primacy should be avoided "This is the first meta-analysis of primary patency at 24 months and access circuit primary patency outcomes".

REVIEWER	Kitrou, Panagiotis University of Patras, Interventional Radiology
REVIEW RETURNED	14-Nov-2020

GENERAL COMMENTS	The current manuscript is a meta-analysis on the use of covered stents for the treatment of dysfunctional AV access. The authors missed the Viabahn study by Rajan et al. (Radiology) and the RESCUE study. They included only studies dealing with the venous-graft anastomotic (VGA) stenosis, so the study is not about covered stents in AVGs, but covered stents for the treatment of VGA stenosis. Meta-analysis is not of specific interest as the results are, nowadays, common knowledge. The majority of the data have been published previously either in meta-analyses or cost-effectiveness analyses. A more extensive meta-analysis of all the available studies (registries, retro, etc.) would be of interest as it would include both RCTs and real-life experience and a larger population.

REVIEWER	Kimani, Peter University of Warwick, Warwick Medical School
REVIEW RETURNED	19-Nov-2020

GENERAL COMMENTS	The manuscript reads well but with my expertise, I am only able to comment on statistical analysis. It is good to include 95% confidence intervals in the abstract. Article summary: The authors indicate that they could not do subgroup analysis because of heterogeneity. Subgroup is usually

	performed when it is thought there is heterogeneity that could be explained by some study characteristics and so I found this reason not convincing. Figure 1: Some numbers are not adding up (records screened, records excluded and records assessed for eligibility). Possibly because of the ongoing trial. If so, it took me time to figure this and so it may be better to have a box on the left. Methods: The methods do not describe how summary characteristics from multiple studies are pooled. For example, it is not indicated how the overall mean ages, standard deviations and p-value comparing mean ages for the two groups are obtained. Same comment for the other study characteristics, including binary. Fixed-effects meta-analysis. I did not find the reason for using fixed-effects meta-analysis model compelling. For example, I would not consider percentages of males in different studies similar. And indeed, tests for heterogeneity in some meta-analysis (e.g. see Figure 3) indicate significant heterogeneity and hence random-effects meta-analysis models may be more appropriate. Also, in general, I consider whether to perform random-effects or fixed-effects meta-analysis considering other factors as well (not just those recorded from patients) such as setting (for example, I would go for random-effects if there are single centre and multi-centre studies since I would not want to assume there is no heterogeneity in such studies). Therefore, I think random-effects is most appropriate in this work. Table 1: For easier comparisons between studies, it would be helpful to report proportions (or percentages) for binary characteristics such as gender. It would be good to have a table describing for each study whether various outcomes' data were collected at each of 6, 12 and 24 months. This will help readers to know why studies are not included in some meta-analysis. There is discrepancy between the results in Figure 3 and the description of the results in the main text. Figure 3: I prefer the forest include results for studies with zero weight (however, no studies will have zero weight if authors use random-effects meta-analysis). I do not see the point of sensitivity analysis of removing a small study in a fixed-effects meta-analysis. As the authors also observed, it is obvious results will not change much since the weight of a small study may be negligible in a fixed-effects meta-analysis. Conclusion, line 1: There is a missing word (or words).

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
Dear Dr. Kennedy, thank you for your kind comments.

A) We have considered and included some of the aforementioned literature and stated that the current literature on drug-eluting or coated devices have, thus far, shown conflicting results and more research is needed to compare these devices with current interventions.

B) W have reported the complications in each arm of every trial, wherever available, in the Supplementary Tables.

C) Where possible, we have also included the arteriovenous access characteristics and how patency was assessed at each time point in each study.

D) Thank you for raising this issue. We only cited the AveNEW trial because it is a trial comparing covered stents (Covera) versus percutaneous transluminal angioplasty alone, which fit our inclusion criteria in our initial protocol. We are aware of AVeVa as an ongoing trial, but this study is a single-arm prospective trial not randomised to percutaneous balloon angioplasty. As such, it has not met our protocol inclusion criteria and has been deliberately excluded from our study.

E) Thank you for pointing out this important point to clarify. Various studies have employed different terminology with the same meaning which initially impeded data extraction. For example, some studies opted the use of anatomic success instead of technical success, which has essentially the same meaning. Given this is a general journal, we have now listed what terms each study used for clarity to readers who are not well-versed in the field (supplementary Table 1). In addition, the heterogeneity in the protocols used for each time point of the trial has been elaborated (Supplementary Table) as per Point C in your comments.

F) In table 1, stent brands were already broken down in each trial.

G) We have changed the wording to: "The applicability of our meta-analysis may be limited because almost every study included focused on AV grafts, whereas in clinical reality, many patients have AV fistulae for access".

H) We have removed this statement.

Reviewer 2
Dear Dr. Kitrou, we thank you for constructive comments and raising a very important point on cephalic arch stenosis.

We are aware of Rajan et al. paper which focused only on cephalic arch stenosis in patients with brachiocephalic fistulae, as it was a sufficiently different but significant entity. As you would know, the predisposition of high flow rates of brachiocephalic fistulae, anatomical features of cephalic arch meant that the cephalic arch is more prone to shearing and subsequently stenosis and thrombosis. Therefore, we have initially excluded it, as per our protocol. The stenoses for most other studies included fall outside the cephalic arch as they are all focused on AV grafts (supplementary Table 2) except the AveNew trial. Nevertheless, this ongoing trial, which only included patients with AV fistulae, has a substantial number of patients with cephalic arch lesions (n= 78, 54.9% in covered stent group; n=70, 50.7%). Therefore, whilst we have now included Rajan et

al. in our systematic review, we are not able to perform meaningful meta-analysis on it due to the lack of focused studies on cephalic arch stenosis. Further research is warranted which would come in the form of the promising AveNew trial.

We have maintained to exclude Falk's RESCUE trial as it is only focused on in-stent restenosis.

We acknowledge the field of interventional radiology is fast-moving. While there may be older meta-analyses that described these, we have clearly stated reasons on what our meta-analysis added, as well as the limitations of previous meta-analyses on this topic. While there are reviews and cost-analysis studies, no specific meta-analysis has formally meta-analyse long-term 24-months outcome.

Including retrospective studies or adding other studies with evidence grade below that of randomised control trials to simply increase numbers would not improve on the quality meta-analysis, and these studies were specifically excluded from our study protocol for that exact reason.

Reviewer 3
Dear Dr. Kimani, thank you for your expert opinion on our manuscript's statistics. We have addressed all of your comments below.

1. We have included the 95% confidence intervals in our abstract.

2. We have not performed a subgroup analysis to compare patency rates of different stents head-to-head because each stent graft trial had different conditions, patient populations, and different endpoints. For example, the FLAIR trial had protocols that required angiograms at two and six months. This rendered the trial to be more meticulous than others which is reflected in their lower reported patency rates (Supplementary Table 4).

3. We have updated Figure 1 to clarify this – you are correct in stating that this was due to the ongoing trial. We have further added another study based on another reviewer's comment.

4. We have updated the Methods section to describe how pooled characteristics mean and standard deviation were calculated.

5. Thank you for providing a compelling rationale of why random-effects model should be used. We have discussed this and agreed with your comments. Subsequently our analysis has now changed to a random-effects model.

6. We have added percentages for binary characteristics in Table 1.

7. For clarity, we have added a supplementary table for each study to state what outcome data (mainly primary patency and access circuit patency) were collected at six, 12, and 24 months. We have also specifically stated what terms the authors used in the table to describe primary patency. Loss of primary patency and loss of access circuit patency were calculated from these outcomes (described in Methods).

8. As per point 5, we have now used random-effects model for our meta-analysis.

9. We agreed with your comments that the sensitivity analysis is redundant and have removed it.

10. The conclusion has been amended to read correctly.

VERSION 2 – REVIEW

REVIEWER	Kennedy, Sean McMaster University
REVIEW RETURNED	09-Jan-2021

GENERAL COMMENTS	Appropriate response to previously noted revisions. No further concerns.

REVIEWER	Kimani, Peter University of Warwick, Warwick Medical School
REVIEW RETURNED	30-Jan-2021

GENERAL COMMENTS	The authors have addressed my comments comprehensively. I was surprised that results of one study in Figure 3a are not estimable as I thought they should be estimate as there are no zeros in the denominator. Check that the results are accurate.