Peer Review File

Reviewer A:

I appreciate the author's efforts. This study is a review literature that analyzed the incidence of distal stent graft induced new entry (dSINE) and risk factors for the occurrence of the dSINE after total arch replacement with frozen elephant trunk technique for aortic dissection. However, this study may not reach an acceptable level for this journal because of inadequate analyses.

The authors described the purpose of this study that assessed the incidence of dSINE and risk factors for occurrence of the dSINE after frozen elephant trunk for aortic dissection. However, there were no detail of assessments about factors associated with dSINE in the results section. The authors should analyze the risk factors for dSINE by statistical analysis more precisely. In also the results of Bologna, the authors should evaluate the risk factors for dSINE by using factors, such as size of the open stent graft, ratio of the open stent graft and native aorta that deployed the open stent graft, angle of the open stent, and et al.

Reply to reviewer A:

Thank you for your kind observation. The primary aim of the review was to define the incidence and the intervention rate of dSINE ("The primary aim of this review was to define the d-SINE incidence and reintervention rate. Then, an analysis of risk factors and supposed predictors for the occurrence of this condition has been performed.").

An extensive scan of literature was performed aiming to detect the supposed risk factors for the development of dSINE after TAR with FET technique. However, only seven articles have been found on this specific topic. Such a little amount of material regarding this topic, collecting data that differ from each other significantly, made a systematic comparison impossible to conduct. Therefore, provided that it was not possible to perform a statistical analysis of the supposed risk factors, we reported only a descriptive analysis. (lines 170-178)

Moreover, our paper aims to display a descriptive representation of the state-of-the-art, and it is not intended as a systematic review analysis.

There is a paragraph on the results in our center, with a risk factor analysis according to the main characteristics of the patients (Table 2).

We implemented Table 2 by displaying the size of the stent graft used. Unfortunately, the collection of data about postoperative Angio CT scans of these patients could not include details such as stent graft angle, which were not available.

Reviewer B

The author wrote a review article on an interesting topic "the dSINE after FET". Only 7 articles are included and afterwards report on own results in Bologna.

I have some questions

Major-revision:
1. The number of articles sought for review is very low. Can you increase this significantly (not only pubmed). There are still enough articles to be found, for example: Osswald (doi: 10.1093/ejcts/ezab297) reports on 149 patients with Debakey I dissection and a dSINE incidence of 9.3% after a follow-up of 2.6 years.

2. In the abstract, you write that you are investigating or showing the risk factors of dSINE as the aim of the study. The risk factor results based on the studies presented have not been shown at all. It has been presented starting only in the discussion. Please write about the possible risk factors in results or remove them from study objective.

Minor-revision:
1. Line 122: Can you please cite this sentence? This contradicts the literature and your writing in the discussion (Line: 171-173). Please clarify

2. The word freedom in Figure 4 is misspelled (Dreedom)

3. (Line 124 and 136): why are this patient not treated?

Reply to reviewer B:
I would like to thank the reviewer for the observations and suggestions that have been provided.
Major-revision
1. We went through a deep review of the literature, and we chose to include only articles that treated specifically dSINE in FET, excluding papers reporting on general FET experience or the occurrence of dSINE in TEVAR. We implemented the article list with further research, not only in PubMed database. We included the article you provided.
2. Thank you very much for your observation. Unfortunately, the articles we found were not enough to perform a systematic meta-analysis to understand the risk factors. We removed it from the aim of the study. However, we reported risk factor analysis according to the Bologna experience and we implemented it according to the suggestions of Reviewer A.

Minor revision
1. We have modified the text to clarify the concept.
2. We have corrected the spelling.
3. These patients have not received treatment according to the small size of the dSINE that was detected. Therefore, they have been treated conservatively by follow-up AngioCT scans.

Reviewer C:

Murana and colleagues presented a literature review about the occurrence of distal stent new entry (dSINE) after total hybrid arch replacement with frozen elephant trunk techniques. The authors emphasized some risk and protective factors from the literature. They also added their personal experience in the manuscript, by providing the freedom of this important complication according to the type of prosthesis used in their institution. They found a higher rate of dSINE when using the Thoraflex graft with respect to the E-Vita open implantation. The manuscript is overall well-written. Some sentences may be improved but without an extensive English revision. Here below my main comments:

1. The aim of the manuscript should be better identified, as the authors provided not only a literature review but also their personal experience.

2. Page 3, line 54: please provide the abbreviation for frozen elephant trunk (FET), as it is the first time that it's used throughout the text.
Page 3 line 55: "(…) although good results (…)".
Page 3 line 58: "(…) even if the etiology remains (…)".
Page 3 lines 58-60: "Endovascular extension or secondary hybrid approach are often planned due to disease progression (…)".
Page 3 lines 72-73: "(…) dSINE is not an emergent condition but remains a relatively frequent complication, occurring in 15 to 18% of the patients (…)".
Page 3, line 73: "(…) after FET focused the attention (…)".

3. Page 4, line 79. I would emphasize in this section that the ambition of the authors was not only to review the current literature but also to provide their own experience with this issue, in a descriptive and retrospective single-center observation.
Page 4, line 99: please provide the abbreviation for EKG-gated.
Page 4, line 103: "(…) reconstruction allow a more realistic measure of aortic diameters (…)".
Page 4, lines 107-108: "(…) the "degeneration" of the stent graft (…)".

4. I would put the difference between dSINE and endoleak also in the introduction part, as it may improve the comprehension of the text or the reader.

5. In the Method section, I miss the statistical approach to analyze the freedom of dSINE in their population. I assume that the authors used the Kaplan Meier Method, but this aspect has to be defined in the method section of the manuscript.

6. Page 5, line 119: what was the abbreviation TAR used for? Total Arch Replacement?
Page 5, line 120: I would add a reference to the Standford classification.
Page 5, line 123: "(…) Only few patients with the diagnosis of dSINE were managed with a conservative approach (…)".

7. Do the authors have information on baseline characteristics of the patients (sex, age,

comorbidities….)? It should enhance the text.

8. Page 6, lines 132-133: Did the patients presenting a dSINE present any symptom? I would add to the manuscript that all these patients were asymptomatic, or in cases of clinical relevance, which were their symptoms.

9. I would begin the discussion section with a little summary of the major findings of the work.

10. Why did the authors not perform a logistic regression, allowing the identification of risk factors for dSINE? Is it by lack of data? Please make this aspect clearer in the manuscript or in the "limitations" paragraph.

11. Page 6, lines 147-149: "(…) in aortic dissection is considered (…) In a chronic setting, it is assumed as " (…)".

12. Page 7, line 158: "(…) develop dSINE, as the landing zone is not in a straight portion (…)".

13. I would make more paragraph in the discussion, to improve the readability of this section.

14. Page 7, line 167: "(…) acute setting, while it becomes stiffer, thicker (…)".
Page 7, line 175-177: (…) In a study performed by Sun and coll. over patient treated with hybrid elephant trunk TAR for either acute or chronic type A aortic dissection, this proved itself a valid technique, with better outcomes than endovascular treatment (…)". Please rephrase

15. Page 8, line 185: "(…) A less rigid, more flexible design may be (…)".
Page 8, line 192: "(…) According to the observation paid? (…)". I suppose that this is a spelling error?
Page 8, line 203-204: I would remove "(…) A proper pre-operative planning at the time of surgery can reduce this complication (…)"; as the current manuscript does not focus on the pre-operative planning but more on the device they used. Maybe another possible conclusion would be that more studies should be made to determine which materials fit for which patients in order to decrease the rate of post-FET dSINE.

16. In the 7 articles identified by systematic review, are the authors able to provide the potentials risk factors for dSINE in each publication? The Table 1 may benefit of an additional column with this information.

17. Table 2. Please provide a definition for zone 2 and zone 2.

18. What were the criteria in Bologna for using the Thoraflex or the E-Vita?

19. Table 3. " (…) Vascutek L, Inchinnan, United Kingdom (…) ". I would also add the advantages and drawbacks of each material in this table, in order to have a more schematic visions of all materials used in this issue.

20. I would add the recent article from Jubouri et al (Jubouri et al. Incidence of Distal Stent Graft Induced New Entry vs. Aortic Remodeling Assosiated with Frozen Elephant Trunk. Front Cardiovasc Med 2022 Mar 10;9:875078. Doi: 10.3389/fcvm.2022.875078) in the discussion section, as they ambitioned also to compare different FET devices available commercially with respect to the occurrence of post-operative dSINE.

Reply to reviewer C:
I would like to thank the reviewer for the observations and the precious suggestions that have been provided.

1. We implemented the aim of the study according to the observation.
2. Thank you very much for the observation, we modified the text accordingly.
3. Thank you very much for your suggestions, we modified the text accordingly.
4. Thank you very much for your observation, we have provided the definition of endoleak to clarify the concept to the reader. (Lines 69-71).
5. Thank you very much for your suggestion, we have implemented the information required in the text. (Lines 103-104).
6. TAR stands for Total Arch Replacement (line 132). The abbreviation has been defined in the manuscript. We have implemented the reference inherent to Stanford classification and modified the manuscript according to the observation that have been paid.
7. It was not the primary aim of this review article. Unfortunately, it will take too much time to undergo all the characteristics of the patients. We will perform another study focusing just on our experience.
8. Thank you very much for your observation; all our patients who developed dSINE have been reported asymptomatic.
9. Thank you very much for your suggestion; we added a paragraph summarizing the major findings of our review. (lines 155-160).
10. Thank you very much for your suggestion; we added a paragraph displaying the limitations of our study. (lines 222-227).
11. Thank you very much for the observation, we modified the text accordingly. (lines 161-162).
12. Thank you very much for the observation, we modified the text accordingly. (lines 171-172).
13. Thank you very much for your suggestion, we edited the text as suggested.
14. Thank you very much for the observation, we modified the text accordingly. (line 181); (lines 190-196).
15. Thank you very much for the observation, we modified the text accordingly. (line

202); (line 209); (lines 203-204).

16. Thank you very much for the observation, we modified table 1 accordingly by adding a column displaying the supposed risk factors. We also added two additional columns ("Pathology" – and "Type of Stent").

17. Thank you very much for the observation, we implemented table 2 with zone 2/3 characterization according to Ishimaru's aortic map.

18. In Bologna we prefer to use Thoraflex device for its ease of deployment. We choose to implant E-vita graft when a longer stent coverage in descending aorta is needed.

19. Thank you very much for your suggestion, we modified table 3 accordingly.

20. Thank you for your suggestion, we appreciated it very much. We have chosen not to include reviews in our paper because of the difficulty in retrieving specific data. We have checked the bibliography of the review published by Jubouri and provided accordingly. We included the paragraph of their findings in our discussion. (lines 216-224).

Reviewer D

This is a timely review on the incidence, mechanisms, and preventive methods of distal stent-graft induced new entry (dSINE) after the frozen elephant trunk operation (FET), an emerging problem of surgery for aortic dissection. Since the review of 7 case series did not provide data on the mechanisms and preventive methods, current manuscript format does not seem appropriate; most of discussions are not directly related with the results of 7 case series review. I would suggest the authors to reformat the manuscript to have several sections that respectively discuss the follow-up protocol, incidence and timing of onset, risk factors, suggested mechanisms (including mechanical properties of the devices), and preventive measures (oversizing, length, etc.). Results of the review of 7 case series should be discussed in the incidence and risk factors section. The Bologna results should be discussed in the follow-up protocol, incidence, risk factors, and mechanism section.

Bologna protocol

The authors advocated contrast-enhanced EKG-gated CT to detect dSINE at 3, 6 12 moths postoperatively and annually thereafter. Since it renders the patients at risk of contrast medium-related complications, such as anaphylaxis and nephropathy, and exposes them to extra-dose of radiation, the adequacy of such a follow-up protocol should also be discussed from the standpoint of adverse effects. I prefer replacement with plain non-gated CT at several points and at long-term follow-up.

Results

The information on the mean interval between surgery and the diagnosis of dSINE is useful. In the review of 7 case series, it was 13-18 months, while it was 27 months (median 20 months) in Bologna. How do the authors explain the observed difference?

How does this information influence the imaging follow-up protocol in Bologna?

3. Although chronic aortic dissection has been reported to be a risk factor of dSINE, it is stated that the majority of dSINE occurred in patients who had undergone FET for acute type A aortic dissection in the literature review section (no data shown). On the other hand, the incidence of dSINE was higher in chronic aortic dissection (including residual type A) in Bologna. What do the authors think is the reason for this inconsistency?

4. Although not new, the observed difference in the incidence of dSINE between Thoraflex and E-Vita in Bologna is valuable. Please add discussion with their own data in the first paragraph of page 9.

Discussion
To discuss the oversizing ratio, it is crucial to state what is the denominator. One cannot determine the real aortic size immediately before the onset of aortic dissection. In addition, there are many methods of measuring the true lumen size, which do not necessarily yield the similar results.

Reply to reviewer D:
I would like to thank you for your precious comments. Unfortunately, the lack of articles found on this specific issue, associated to a heterogeneous amount of data, made it difficult, almost impossible, to perform a statistical analysis of the supposed risk factors for dSINE development. However, we tried to implement it as a descriptive analysis. (lines 170-178). This aspect has been clarified in "limitations" paragraph. (Lines 222-227)

Bologna protocol
We appreciate the observation made by reviewer D. However our Angio CT follow-up protocol is based on the consensus document on acute type A aortic dissection (Malaisrie S.C. et al - 2021 The American Association for Thoracic Surgery expert consensus document: Surgical treatment of acute type A aortic dissection. The Journal of Thoracic and Cardiovascular Surgery, 162(3), 735–758.e2.) which recommend EKG-gated, AngioCT scans predischarge, in addition to 6- and 12-months scans. ("…We suggest that if the renal function permits, predischarge CT or MRI should be performed in addition to scans at 6 months and 1 year. These studies are best performed in multiple phases including noncontrast, arterial phase, and delayed venous phase modes of acquisition to allow for a more com- plete assessment of false lumen perfusion…") We implemented it in the reference section as well as in the text.

Results
As previously described, we follow a strict protocol of Angio CT scans in follow up. Maybe we detect SINEs later because of different criteria in size selection in TAD, as we do not oversize the diameter of the stent, and in chronic dissection, we do not exceed a 20 percent oversizing. Moreover, this finding does not have any influence on our

follow-up protocol; in fact, as we have made clear before, we follow the recommendations according to the consensus document.

"Although chronic aortic dissection has been reported to be a risk factor of dSINE, it is stated that the majority of dSINE occurred in patients who had undergone FET for acute type A aortic dissection in the literature review section (no data shown). On the other hand, the incidence of dSINE was higher in chronic aortic dissection (including residual type A) in Bologna. What do the authors think is the reason for this inconsistency?"
Reply: We clarified the data in Table 1 and we eliminated the sentence from the text. Anyway, that inconsistency might be explained by a bias due to the pathology itself. In fact, patients with acute type A aortic dissection have shorter follow-up times due to adverse events.

"Although not new, the observed difference in the incidence of dSINE between Thoraflex and E-Vita in Bologna is valuable. Please add discussion with their own data in the first paragraph of page 9."
Reply: Thank you for your suggestion. We implemented it in the first paragraph of the discussion section. (lines 158-162).

Discussion
Thank you for your observation. We described what is reported in the article referenced as n.3 (Czerny M, Schmidli J, Adler S et al. Current Options and Recommendations for the Treatment of Thoracic Aortic Pathologies Involving the Aortic Arch: An Expert Consensus Document of the European Association for Cardio-Thoracic Surgery (EACTS) & the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg. 2019;55(1):133-62.).
Furthermore, we added a paragraph on the criteria that are adopted in Bologna to measure the diameter of the TL. (Lines 113-116) (188-191).

Reviewer E:
The authors provide a manuscript on distal stent graft induced new entry (dSINE) after frozen elephant trunk (FET). dSINE is a FET or stentgraft-related complication and remain an important issue after total arch replacement with FET. I appreciate authors' effort to review this important complication.
However, I have several concerns and questions as following:
1. In Bologna, how have you determined the size of FET in acuter and chronic dissection respectively? Specific percentages to the whole aorta or the true lumen would be helpful for readers.

2. After reviewing manuscripts, what do you think is important to prevent dSINE? Most surgeons have been careful to avoid oversizing but the incidence rates of dSINE was reportedly high.

3. (line 129) How did you decide the type of FET, Thoraflex or Evita Open, in Bologna?

4. (line 62) Reference number is needed (manuscript by Dong et al.).
5. (line 203) According to the reference #23, "25 %" was the incidence of SINE after TEVAR, not mortality rates.

6. (Figure 4) Freedom, not Dreedom, is correct.

Reply to reviewer E:
1. I would like to thank you for your precious comments. In the acute setting, we do not perform any oversizing. In chronic aortic dissections we estimate the distal landing zone diameter by measuring the MPR CT images, starting from zone 2 according to Ishimaru aortic map, then, after having selected the proper stent length, we calculate the true lumen perimeter/diameter at the estimated site of the distal end of the stent.

2. In relation to the second observation, we still believe that the stent graft oversizing, along with the stent length, is the most important risk factor for the development of dSINE.

3. In Bologna we prefer to use Thoraflex device for its ease of deployment. We choose to implant E-vita graft when a longer stent coverage in descending aorta is needed.
4. We provided the reference number accordingly.
5. We modified it accordingly by correcting the reference number.
6. We provided the right spelling.