Author’s response to reviews

Title: Self-expanding nitinol stents of high vs. low chronic outward force in de-novo femoropopliteal occlusive arterial lesions (BIOFLEX-COF trial): study protocol for a randomized controlled trial

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Author’s response to reviews:

Reviewer #1:

Complex study, well elaborated, with few methodological items to be reviewed!

The authors design the study as prospective, monocentric, randomized, but I suggest that they rethink the possibility of calling a prospective, quantitative, randomized cohort study.

Answer:

Changes in study design description have been made in methods section (abstract and full article). It is now called a “prospective, quantitative, randomized cohort study” as suggested by Reviewer #1.

In the objective item the authors explain the objective and after, in the same item, explain other details that are not part of the objectives. I suggest redirecting this explanation to another item in the methodology and leave only the sentence about the main purpose.

Answer:

Methods section has been edited. There is now a section called “stent types” which describes the two stent types in detail. The objective of the study is now only mentioned before the initiation of methods as wished by reviewer #2.

Reviewer #2:
"Lastly, there exists not a single randomized study comparing primary nitinol 56 stenting versus drug-covered balloon angioplasty to this day and a historic comparison of study collectives shows similar results."

- Please rephrase sentence

- The last part of the sentence does not make any sense. If you refer to results from other studies, please insert reference.

Answer:

Last part of the sentence has been removed. Now there is only written: “Lastly, there exists not a single randomized study comparing primary nitinol stenting versus drug-covered balloon angioplasty to this day.”

Why is this "objective" section written after the initiation of methods? It should be before methods. Because now it seems that objectives are a part of methods section.

Answer:

The “objective” section in the “methods” section has been removed. There is now a new section in the “methods” part called “stent types” which describes the two stent types in detail. The main objective of the study is now only mentioned before the initiation of methods.

Symptom driven angiography is reported as your secondary endpoint in your flowchart (figure 3), however not mentioned in the description of methods. Please be clear about your primary and secondary endpoints/objectives.

Answer:

Figure 3 has been edited: “symptom driven angiography” has been changed to “target lesion revascularization (TLR)”, consistent with the description of methods.

The Rutherford Classification and Walking impairment questionnaire (WIQ) are mentioned without explaining the reason to be included. Please be precise regarding this part of description.

Answer:

The section about Rutherford Classification and Walking impairment questionnaire (WIQ) were removed from the study protocol, since it does not lie within the focus of this study.

Your randomization procedure should be more precise, the description is lacking.
Answer:

Description of randomization procedure has been updated. Block randomization on a one-to-one basis is performed using an online randomization program (www.sealedenvelope.com).

In the section of "follow up", you refer to figure 3 about details of clinical assessment, however that is not true. No specific information are gathered from figure 3. Please change your figure 3 if you want to refer to it.

Answer:

The Reference to figure 3 in the “follow up” section has been removed. Now there is only a reference to figure 3 in the study design part (“Figure 3 shows a flow diagram of the study design.”).

Reviewer #3:

This is a RCT of high scientific and clinical interest for those who do endovascular treatment of PAD. The manuscript is well written. Some information to understand the study is missing as described below.

Abstract:

Companies of the 2 different stents should be mentioned

Answer:

now mentioned in the abstract

Methods:

The mechanical characteristics of the 2 different stents (COF, hoop stress, struts diameter etc.) should be described in more detail to understand, why these 2 stents were selected.

Answer:

Mechanical characteristics of the two stents (RRF, COF, strut diameters) were added to the manuscript (section “stent types”). Hoop stress as a variable is used for balloon expandable stents, for self-expandable stents RRF is the equivalent variable.

The method of CTA should be described in detail. How do you reduce metal blooming artifacts?
Answer:

Method of CTA and how we reduce blooming artifacts is now described in detail in the section “CTA”.

Calculation of patient number is missing. Why 80 patients? What is the expected difference between 2 arms at primary endpoint, estimated dropouts.

Answer:

As for the calculation of patient number, in the section “statistical analysis” we describe the sample size calculation in detail: “Sample size calculation is based on the primary endpoint at one and two years represented by the percentage of in-stent neointima formation (relative to the stent diameter). Statistical significance between the groups will be tested using a t-test at a level of significance of 0.05. To detect a difference of 0.8 standard deviations with a statistical power of 90%, a sample size of 34 patients in each group is required. With a maximum dropout rate of 15%, 40 patients will be randomized per group.”

Discussion:

It should include the difference of clinical results between nitinol stents with high COF such as Lifestent and low COF such as Pulsar stent or Supera stent.

Answer:

No prospective direct comparison has yet been made in the literature to address differenced in COF between different stent types, now mentioned in the discussion.

Without solicitation 2 minor amendmants have been made in the protocol description:

1. Some specifications in the inclusion and exclusion criteria were added (inclusion criteria – clinical point 3 and exclusion criteria point 15).

2. Section “Procedure”: One sentence was specified. One sentence changed to be more precise. The minimum time span for Clopidogrel 75mg p.o. QD post-procedure was changed from two to three months to comply with the clinical standard at our institution.

3. To comply to SPIRIT guidelines some minor amendments were added.