PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Carbon dioxide flushing versus saline flushing of thoracic aortic stents: protocol for a multicentre pilot randomised controlled trial
AUTHORS	Crockett, Stephen; Hanna, Lydia; Singh, Abhinav; Gunning, Stephen; Nicholas, Richard; Bicknell, Colin; Hamady, Mohamad; Gable, Dennis; Sallam, Morad; Modarai, Bijan; Abisi, Said; Lyons, Oliver; Gibbs, Richard

VERSION 1 – REVIEW

REVIEWER	Mylonas, Spyridon N. University of Cologne, Department of Vascular and Endovascular Surgery
REVIEW RETURNED	09-Oct-2022

GENERAL COMMENTS	The authors are planning a pilot randomised study aiming to investigate the role of carbon dioxide flushing vs saline flushing of thoracic stentgrafts for reducing cerebral embolic events. Hereby are my comments As the authors describe, the discrimination of solid emboli vs gaseous ones is difficult. Is there a method of evaluating the atherosclerotic burden of the aortic arch in order to obtain more homogenous cohort regarding this potential confounder? Here a stratification by the treated pathology (aneurysm vs dissection vs traumatic transection) would be of interest. The Fazeka's scale is widely used to quantify the WM lesions attributed not only to small vessel ischemia (i.e., demyelination). Given that you are planning to perform the clinical assessment preoperatively, it would be quite helpful to plan a preoperative DW MRI in order to increase the robustness of your results. Could you please elaborate where the estimation of biomarkers will be conducted? On site or will be a core labor which will undertake the measurements? The same for the imaging analysis. You describe " Participants and outcome assessors will be blinded to group allocation."

REVIEWER	Hakovirta, Harri University of Turku Faculty of Medicine, Surgery
REVIEW RETURNED	01-Nov-2022

GENERAL COMMENTS	The present study protocol "Carbon dioxide flushing versus saline

	flushing of thoracic aortic stents for cerebral embolic protection in thoracic endovascular aortic repair (INTERCEPT): protocol for a multicentre randomised controlled trial" has a significant impact on neuroprotection during TEVAR procedures. The "silent" cerebral infarction (SCI) is known to associate with TEVAR procedures and might have serious consequences for affected patients. If carbon dioxide flushing can have positive effect on SCI lacks scientific evidence. Abstract: Methods and analyses The causes for TEVAR implantation should be defined clearly also in the abstract aneurysm, dissection, trauma or even all causes. Lines 58-59 stratified according to landing zone. Has this been considered in power analyses (60 per group)? Ethics and dissemination Page 3 lines 13-14 The committee or institution providing the ethical approval should be stated (both UK and New Zeeland), for UK number of approval missing. Registration number for ClinicalTrials exists and number for New Zeeland. At page 11 lines 9-20 institutions are nicely presented, but the approval numbers are missing for both UK and NZ Page 3 line 40 "Patient and Public involvement" should the important aspect – patients are told to be able to stop participation at any time without any consequence and be treated according to normal treatment protocol? Page 5 lines 37-38 something missing in the statement? Should be revised to be more readable. Page 6 line 50-> The definition for patient selection would make section more accurate. Even mentioning patients regardless of aortic pathology or similar would be fine if this is the case. This can be found nicely from Box 2 but should be clearly in the main text. Page 7 lines 10-14. Has the effect of stratification to the landing zones been included while sample size was calculated? Page 8 lines 43-55 the same issue. Authors have calculated the sample size based on earlier results nicely 38/group. Then, since there are 5 landing zones, it is hard to understand how estimated 10-12/landing zone is ok (also estimated 20% drop-out rate for MRI).

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Spyridon N. Mylonas, University of Cologne
Comments to the Author:
The authors are planning a pilot randomised study aiming to investigate the role of carbon dioxide flushing vs saline flushing of thoracic stentgrafts for reducing cerebral embolic events.

Hereby are my comments
As the authors describe, the discrimination of solid emboli vs gaseous ones is difficult.
Is there a method of evaluating the atherosclerotic burden of the aortic arch in order to obtain more homogenous cohort regarding this potential confounder? Here a stratification by the treated pathology (aneurysm vs dissection vs traumatic transection) would be of interest.

The Fazeka's scale is widely used to quantify the WM lesions attributed not only to small vessel ischemia (i.e., demyelination). Given that you are planning to perform the clinical assessment preoperatively, it would be quite helpful to plan a preoperative DW MRI in order to increase the robustness of your results.

Could you please elaborate where the estimation of biomarkers will be conducted? On site or will be a

core labor which will undertake the measurements? Brief paragraph on p.9 to describe this. Not done in too much detail for word count reasons. The same for the imaging analysis. You describe " Participants and outcome assessors will be blinded to group allocation."

Reviewer: 2
Dr. Harri Hakovirta, University of Turku Faculty of Medicine
Comments to the Author:
The present study protocol "Carbon dioxide flushing versus saline flushing of thoracic aortic stents for cerebral embolic protection in thoracic endovascular aortic repair (INTERCEPT): protocol for a multicentre randomised controlled trial" has a significant impact on neuroprotection during TEVAR procedures. The "silent" cerebral infarction (SCI) is known to associate with TEVAR procedures and might have serious consequences for affected patients. If carbon dioxide flushing can have positive effect on SCI lacks scientific evidence.
Pilot is based on previous benchtop modelling showing reduced air released from stents when using CO2 flushing. Non randomised cohort study from LH, has been shown to reduced the size and frequency of infarcts when using CO2 flushing.

Abstract: Methods and analyses The causes for TEVAR implantation should be defined clearly also in the abstract aneurysm, dissection, trauma or even all causes.
Please see p.2 – "TEVAR is offered as preventative treatment to prevent rupture and death from aneurysmal aortic disease, aortic dissection and traumatic aortic injury"

Lines 58-59 stratified according to landing zone. Has this been considered in power analyses (60 per group)?
Yes- that is why the study is overpowered. Sample size calculation was 76 patients, but as 5 zones of TEVAR, was felt we should aim for 10-12 per group, giving us a sample size calculation of 120.

Ethics and dissemination
Page 3 lines 13-14 The committee or institution providing the ethical approval should be stated (both UK and New Zeeland), for UK number of approval missing. Registration number
for ClinicalTrials exists and number for New Zeeland.
These have now been included

At page 11 lines 9-20 institutions are nicely presented, but the approval numbers are missing for both UK and NZ
Included
Page 3 line 40 "Patient and Public involvement" should the important aspect – patients are told to be able to stop participation at any time without any consequence and be treated according to normal treatment protocol?
Edited as recommended
Page 5 lines 37-38 something missing in the statement? Should be revised to be more readable.
Unsure which statement you mean.
Page 6 line 50-> The definition for patient selection would make section more accurate. Even mentioning patients regardless of aortic pathology or similar would be fine if this is the case. This can be found nicely from Box 2 but should be clearly in the main text.
Not sure this is necessary. This is a box for randomisation details, indication is already described in box 2
Page 7 lines 10-14. Has the effect of stratification to the landing zones been included while sample size was calculated?
Yes
Page 8 lines 43-55 the same issue. Authors have calculated the sample size based on earlier results nicely 38/group. Then, since there are 5 landing zones, it is hard to understand how estimated 10-12/landing zone is ok (also estimated 20% drop-out rate for MRI).
We have intended for this to be an overpowered study based on stratification to landing zones.

VERSION 2 – REVIEW

REVIEWER	Mylonas, Spyridon N. University of Cologne, Department of Vascular and Endovascular Surgery
REVIEW RETURNED	05-Jan-2023

GENERAL COMMENTS	The authors have extensively revised the manuscript according to the Editor's and Reviewer's suggestions increasing the quality of the paper.

REVIEWER	Hakovirta, Harri University of Turku Faculty of Medicine, Surgery
REVIEW RETURNED	14-Jan-2023

GENERAL COMMENTS	Revised according given comments