Peer Review File

Article information: https://dx.doi.org/10.21037/jtd-21-1591

Reviewer A

Comment 1: The detail of cerebral perfusion was unclear. They stated selective antegrade cerebral perfusion, but which neck vessels were perfused and how much volume were given during cerebral perfusion. This is the most important factor to prevent perioperative stroke.

Reply 1: Thank you for this important question. We agree with the reviewer that cerebral perfusion is a crucial technique to prevent perioperative stroke in aortic surgery. If selective antegrade cerebral perfusion was applied in our center, we perfused the carotid artery uni- or bilateral depending on the distal extension of the pathology. We added parameters concerning cerebral perfusion to the table of our univariate analysis (e.g. cerebral perfusion flow, volume, and temperature; see table 3). Since bilateral cerebral perfusion showed a significant difference between the two groups, we performed logistic regression analysis adding this parameter to our risk factor model. It was neither identified as an independent risk factor nor as a protective factor. Correspondingly, cerebral perfusion under hypothermic circulatory arrest did neither show statistical significance in the multivariate model. The reason for cerebral perfusion not being identified as a protective factor remains unclear. Nevertheless, the analysis may be biased by the strong overlap of patients undergoing total arch replacement and SACP. As total arch replacement was identified as a strong risk factor for postoperative stroke, this may have statistically reduced the protective effect of cerebral perfusion.

Changes in the text: We modified table 3 and added the parameters unilateral cerebral perfusion, bilateral cerebral perfusion, hypothermic cerebral arrest, cerebral perfusion flow, cerebral perfusion volume, cerebral perfusion temperature, and cerebral monitoring. (see page 32, line 593, table 3)

Comment 2: How many patients did have preoperative cerebral malperfusion in the type A dissection case? Preoperative malperfusion was associated with the incidence of perioperative stroke?

Reply 2: Thank you for this interesting and relevant question. Of all 240 patients with acute type A dissection, 45 (18.8%) showed preoperative cerebral malperfusion. Of these, 9 suffered from a postoperative stroke. Other reviewers and the authors found it interesting to conduct a subgroup analysis of type A dissection cases since the stroke rate of 15.8% is very high in these patients. Here, neither in the univariate nor in the multivariate analysis, preoperative cerebral malperfusion was associated with the occurrence of a postoperative stroke.

Changes in the text: We included a subgroup analysis of all patients suffering from acute type A dissection in the supplementary material to identify group-specific risk factors (see tables S11-15). Here, no significant independent risk factors could be identified (see page 15, line 262).

Comment 3: Why the stroke rate was increasing if the ECC time got longer? I think the appropriate brain protection should not affect perioperative stroke if it got longer.

Reply 3: Thank you for this important comment. We agree that adequate brain protection strategies should prevent postoperative stroke. However, high cardiopulmonary bypass time is reported to be an independent risk factor for postoperative stroke after cardiac surgery (1-4). Besides other reasons, long duration of cardiopulmonary bypass considerably affects the whole body by causing inflammation and coagulopathy (5). Emboli formed by activation of the hemostatic system due to inflammation may cause focal neurological deficits (6). Varying mean arterial blood pressure during cardiopulmonary bypass can have further negative effects on the cerebral function by causing either hyperperfusion-linked brain edema, or by cerebral hypoxia via hypoperfusion (7).

In both univariate and multivariate analysis, high ECC time was the only operative time to be associated with the occurrence of postoperative stroke. However, this phenomenon might be caused by statistical multicollinearity, as the length of the ECC time correlates with the length of other surgical times (e.g. aortic clamp time or cerebral perfusion time).

We therefore added the possible statistical multicollinearity to the limitation section (see page 22, line 433).

Changes in the text: We added the following text to the limitation section: "Another limitation regarding the statistical analysis is that only high ECC time correlated with stroke. This might be caused by statistical multicollinearity, as the length of the ECC time correlates with the length of other surgical times (e.g. aortic clamp time or cerebral perfusion time)." (Page 22, line 433).

References:

1. Ghoreishi M, Sundt TM, Cameron DE, et al. Factors associated with acute stroke after type A aortic dissection repair: An analysis of the Society of Thoracic Surgeons National Adult Cardiac Surgery Database. J Thorac Cardiovasc Surg 2020;159:2143-54.e3.
2. Chung J, Stevens LM, Ouzounian M, et al. Sex-Related Differences in Patients Undergoing Thoracic Aortic Surgery. Circulation 2019;139:1177-84.
3. Conzelmann LO, Hoffmann I, Blettner M, et al. Analysis of risk factors for neurological dysfunction in patients with acute aortic dissection type A: data from the German Registry for Acute Aortic Dissection type A (GERAADA). Eur J Cardiothorac Surg 2012;42:557-65.
4. Pacini D, Leone A, Di Marco L, et al. Antegrade selective cerebral perfusion in thoracic aorta surgery: safety of moderate hypothermia. Eur J Cardiothorac Surg 2007;31:618-22.
5. Taylor KM. Central nervous system effects of cardiopulmonary bypass. Ann Thorac Surg 1998;66:S20-4; discussion S5-8.
6. Sniecinski RM, Chandler WL. Activation of the Hemostatic System During Cardiopulmonary Bypass. Anesthesia & Analgesia 2011;113:1319-33.
7. Qu JZ, Kao L-W, Smith JE, et al. Brain Protection in Aortic Arch Surgery: An Evolving Field. Journal of Cardiothoracic and Vascular Anesthesia 2020.

Comment 4: You evaluated long-term survival with 30-day and 90-day landmark analysis. I do not recognize this method. Brain protection was most important thing to prevent perioperative stroke. As you stated that once patients had stroke after the

operation, their prognosis was awful. I do not think that 30-day or 90-day survival after the surgery was important for long-term results.

Reply 4: Thank you very much for this relevant remark. We agree that the main message of the survival analysis is that perioperative stroke after aortic surgery is associated with a poor long-term outcome. Nevertheless, the 30-day and 90-day landmark analyses show that this poor outcome is mostly caused by events within the first 90 days after surgery. This leads us to the conclusion that once stroke patients survived the first 90 days after the operation, their prognosis is not significantly impaired compared to patients without postoperative stroke.

However, we agree with the reviewer that the main message is the decreased long-term survival of patients suffering postoperative stroke.

Changes in the text: We added the following text to our discussion: "Summarizing, we conclude, that postoperative stroke is indeed relevant for an impaired long-term outcome. The impaired long-term outcome is mainly caused by events within the first 90 days after surgery. We observed a low rate of recovery in the long-term follow-up. We cautiously conclude that only few patients recover from a severe postoperative stroke after aortic surgery if symptoms remained until hospital discharge." (Page 17, line 310)

Comment 5: What is your strategy for acute type A dissection? All patients underwent hemi-arch replacement? Or patient based strategy? And if you underwent both hemi-arch and total arch replacement, which procedure caused higher incidence of perioperative stroke?

Reply 5: Our surgical strategy in patients with acute type A dissection (ATAD) depends on the age and comorbidities of the patient as well as the localization of the entry and the extension of the dissection in the aortic arch and descending aorta. Recent studies indicated that patients with a primary entry in the distal aortic arch or in the proximal half of the descending thoracic aorta may benefit from a Frozen Elephant Trunk (FET) procedure in the acute situation to treat associated malperfusion syndrome or to avoid its postoperative development (1,2). Therefore, we prefer to perform a FET procedure in this specific sub-cohort in the acute situation in young patients that present hemodynamically stable. This approach is also recommended by the current guidelines of the EACTS and the ESVS on the treatment of aortic arch pathologies (3).

In hemodynamically instable patients, in patients of higher age with relevant comorbidities, and in patients with a dissection of limited extension, we rather perform a hemiarch replacement. Due to chronic residual aortic dissection with persistent false-lumen perfusion, subsequent reinterventions are necessary in about 24% of these patients within 10 years after initial treatment of ATAD (4). However, our group was able to show that this subgroup, if necessary, could later undergo a FET procedure in an elective setting with a comparable low early mortality of 3.2% (5).

Our subgroup analysis showed that of 163 patients undergoing hemiarch replacement for acute type A dissection, 27 (16.6%) suffered from postoperative stroke. Of 62 patients undergoing total arch replacement, 8 (12.9%) had a postoperative neurological deficit. (See supplementary material, page 18, table S12)

Changes in the text: None.

<u>References:</u>

1. Vendramin I, Lechiancole A, Piani D, et al. An Integrated Approach for

Treatment of Acute Type A Aortic Dissection. Medicina (Kaunas) 2021;57.
2. Matt P, Banerjee P, Grapow M, et al. Modified frozen elephant trunk for acute type A aortic dissection: a comparative study with standard repair technique. Eur J Cardiothorac Surg 2017;51:754-60.
3. Czerny M, Schmidli J, Adler S, et al. (2019). 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;57(2), 165–198.
4. Geirsson A, Bavaria JE, Swarr D et al. Fate of the residual distal and proximal aorta after acute type A dissection re- pair using a contemporary surgical reconstruction algorithm. Ann Thorac Surg 2007;84:1955–64.
5. Demal TJ, Bax L, Brickwedel J, et al. Outcome of the frozen elephant trunk procedure as a redo operation. Interact Cardiovasc Thorac Surg 2021; 33(1):85-92

Reviewer B

Comment 1: The authors reported an interesting study about the risk factors for stroke after thoratic aortic surgery.
As they mentioned, identification of risk factors in postoperative stroke is important.
This study was very well-written, but I have several questions.
In the introduction section, they said that the aim of this study was to identify risk factors for new postoperative stroke. However, they also showed the long term survival rate, comparing early and late survival rate between stroke and non-stroke group. I think it would be better to mention it in the introduction section.
Reply 1: Thank you very much for your kind feedback. We absolutely agree that this introduction does not completely represent the study design. We therefore decided to announce the long-term survival analysis in the introduction, as you suggested. We have modified our text accordingly (see page 6, line 91).
Changes in the text: We added the following text to the introduction section: “Moreover, we compared early and late survival rate between the stroke and the no-stroke group.” (Page 6, line 91)

Comment 2: In the methods and results section, definitions of elective, urgent, emergent, salvage were not described. Please describe them in detail.
Reply 2: Thank you for conscientious reading of our manuscript. We have modified our text as advised (see page 8, line 126).
Changes in the text: We added the following text to the methods section: “Urgency statuses were defined according to the EuroSCORE II (11) as
• elective: routine admission for operation;
• urgent: patients not electively admitted for operation but who require surgery on the current admission for medical reasons and cannot be discharged without a definitive procedure;
• emergency: operation before the beginning of the next working day after decision to operate;
• salvage: patients requiring cardiopulmonary resuscitation (external cardiac massage) on route to the operating room or before induction of anaesthesia. This does

not include cardiopulmonary resuscitation after induction of anaesthesia." (Page 8, line 126)

Comment 3: In the methods and results section, the definition of any atherosclerotic entity was not described. Please describe it in detail.
Reply 3: Thank you for pointing this out. As some other definitions, the definition of any atherosclerotic disease could be found in the supplementary material. However, we agree that this is not prominent enough. We therefore moved this definition into the methods section of the manuscript (see page 8, line 134).
Changes in the text: We moved the following text to the main manuscript: "Any atherosclerotic entity was defined as either coronary artery disease in the patient's history and/or extracardiac arteriopathy as defined by the EuroSCORE II." (Page 8, line 134)
Furthermore, we added the following text to the methods section: "Extracardiac arteriopathy includes claudication, carotid stenosis >50%, amputation for arterial disease or preceding or prospective intervention on the abdominal aorta, carotids or arteries of extremities." (Page 8, line 135)

Comment 4: In the methods and results section, they defined the postoperative neurological deficit as present or not. However, stroke has a wide spectrum of severity, and the severity of postoperative stroke is important to evaluate risk factors. Please describe it in more detail. If data were not available, please discuss it in limitations.
Reply 4: We want to thank the reviewer for this very relevant remark. We absolutely agree and therefore included a more profound analysis of stroke severity to the manuscript. In all patients with postoperative stroke, we evaluated the modified Rankin Scale (mRS) (1) as part of the clinical evaluation to estimate the degree of disability caused by the stroke. Furthermore, we distinguished between focal and global neurological deficit and whether the stroke was located in the left or the right hemisphere, or on both sides.
However, we intentionally only included patients with persisting neurological deficits and excluded patients with a transient neurological deficit (transient ischemic attacks or minor strokes), as we clinically observed that especially patients with persistent stroke symptoms show an impaired prognosis.
Changes in the text: We added the following text to the results section:
"In 48.9% (n=46) of the strokes, the ND was considered focal. In 51.1% (n=48) it was considered global. In cranial MRI or CT imaging, lesions were observed in the left and right hemisphere in 17 (20.0%) and 19 patients (22.4%), respectively. In 49 patients (57.6%), both hemispheres were involved. In 9 patients, MRI or CT images weren't available for retrospective analysis anymore. Of all patients suffering from postoperative stroke, we could evaluate the mRS score of 63 patients at discharge. Of these, 79.4% (n=50) had a score of 3 or above." (Page 12, line 194)
Furthermore, we added the following definition to our supplementary material:
"Modified Rankin Scale
0 - No symptoms at all
1 - No significant disability despite symptoms: able to carry out all usual duties and activities

2 - Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance
3 - Moderate disability: requiring some help, but able to walk without assistance
4 - Moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance
5 - Severe disability: bedridden, incontinent, and requiring constant nursing care and attention" (see supplementary material, page 4, line 51-60)

References:
1. van Swieten JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604-7.

Comment 5: In this study, they said that early mortality rate was higher in patients with stroke than those without stroke, and long-term survival rate was not different between the two groups. I think that the severity of stroke also should be discussed to compare the survival rate between early and long term. It would be better to show the data, but if not possible, it should be discussed in limitations.
Reply 5: Thank you very much for pointing this out. We agree that comparing the impact of more and less severe strokes on the long-term outcome is of great interest for the reader. Therefore, we formed two groups of differing stroke severity and compared early and mid-term survival in an non-adjusted analysis. The first group included patients suffering from focal and one-sided neurological deficit (n = 25) and the second group included patients with global neurological deficit or stroke lesions located in both hemispheres (n = 69). This analysis revealed that patients with a more severe stroke (global or both hemispheres) had a higher 30-day (8.0% vs 43.5%; *p*=.001) and one-year mortality (31.3% vs 76.6%; *p*=.001) than the group with a focal and one-sided stroke.
Changes in the text: We added the following text to the results section: "In a non-adjusted analysis, patients with a more severe stroke (global or both hemispheres) had a higher 30-day (8.0% vs 43.5%; p=.001) and one-year mortality (31.3% vs 76.6%; p=.001) than patients with a focal and one-sided stroke." (Page 15, line 278)

Comment 6: Additional English correction is not required.
Reply 6: Thank you very much for your kind feedback.
Changes in the text: None.

Reviewer C
Comment 1: It seems that procedures isolated to the descending aorta were excluded, but that is not explicitly stated. Please include in the methods.
Reply 1: Thank you for this observation. We actually did include descending procedures. However, as isolated descending pathologies are mainly treated using endovascular techniques at our center, open descending replacements are a rare entity in our database (n=9). Furthermore, since we started our Frozen Elephant Trunk (FET) program in October 2010, we completely abstained from isolated open descending replacements.
Changes in the text: None.

Comment 2: Transient (less than 7 days) neurologic deficit and bypass cannula location are buried in the tables. I would include statements about these in the results also as they are important to the reader.
Reply 2: Thank you very much for this good suggestion. We modified the text as advised (see page 11, line 188, and page 12, line 194).
Changes in the text: We added the following text to the results section:
"Of all patients, 2.5% suffered transient ND." (Page 12, line 194)
"The most common site of cannulation was the ascending aorta or the aortic arch (n=903, 67.7%), followed by the subclavian (n=211, 15.8%) and the innominate artery (n=182, 13.6%). In only 34 (2.5%) patients, the femoral artery was cannulated for cardiopulmonary bypass." (Page 11, line 188).

Comment 3: The methods and described models do not support development of a "risk factor model" per se but rather an exploration of "associated variables." This may seem like a semantic issue but it is important.
Reply 3: Thank you very much for pointing this out. We modified the text as advised (see page 9, line 151).
Changes in the text: We changed the corresponding text in the methods section as follows:
"Potential pre- and intraoperative factors (candidates) identified by significant differences in this univariate analysis were further tested using multivariate logistic regression to explore independent variables associated with postoperative stroke." (Page 9, line 151)

Comment 4: The authors are to be commended - this appears to be a large volume. How might volume effects impact outcomes? Does your center have any specific perfusion (e.g. induced hypertension) or other stroke prevention protocols used postoperatively? Do the authors think these results are generalizable to smaller practices?
Reply 4: Thank you very much for this important question. This is a single-center analysis and therefore we are not able to assess the influence of aortic center volume on outcomes. However, in our study, experience of the surgeon was not identified as a predictor for postoperative stroke. This analysis maybe biased as more experienced aortic surgeons rather performed complex aortic arch surgery when compared to non-experienced surgeons. There are some studies suggesting that high volume centers have a preferable outcome in aortic surgery (1-3). However, as valid data on this topic is still scare, we plan to address this scientific issue in future studies using data from the European registry of aortic type A dissection (ERTAAD) (4).
To prevent postoperative stroke in patients that underwent total aortic arch replacement, we use induced hypertension if bleeding risk appears low.
Changes in the text: We added the following text to our limitations section: "Moreover, our data represents the outcome of a high-volume aortic center. It is not certain if these results apply to lower volume centers as well." (Page 22, line 425)
References:
1. Miyata H, Motomura N, Ueda Y, et al. Toward quality improvement of thoracic aortic surgery: estimating volume-outcome effect from nationwide survey. Eur J Cardiothorac Surg 2009;36:517-21.

2. Merlo AE, Chauhan D, Pettit C, et al. Outcomes following emergent open repair for thoracic aortic dissection are improved at higher volume centers in direct admissions and transfers. J Cardiothorac Surg 2016;11:118.
3. Yamaguchi T, Nakai M, Sumita Y, et al. The impact of institutional case volume on the prognosis of ruptured aortic aneurysms: a Japanese nationwide study. Interactive CardioVascular and Thoracic Surgery 2019;29:109-16.
4. Biancari F, Mariscalco G, Yusuff H, et al. European registry of type A aortic dissection (ERTAAD) - rationale, design and definition criteria. J Cardiothorac Surg 2021;16:171.

Comment 5: Did any patients have improvement or resolution of the neurologic deficit on long term follow-up?
Reply 5: Thank you for this question. In patients with postoperative stroke, we evaluated the modified Rankin Scale (mRS) score before discharge and one year after the operation in our aortic outpatient clinic. Unfortunately, mRS score data after one year is only available of 16 out of a total of 22 stroke patients surviving the first year after surgery. At discharge, 79.4% (n=50) of stroke patients had a mRS score higher than 3. One year after surgery, this rate decreased to 68.8% (n=11) of patients with a score higher than 3. We cautiously conclude that only few patients recover from a severe postoperative stroke after aortic surgery if symptoms remained until hospital discharge.
Changes in the text: We added the following text to our results section:
“In patients with postoperative stroke, we evaluated the modified Rankin Scale (mRS) score before discharge and one year after the operation in our aortic outpatient clinic. Unfortunately, mRS score data after one year is only available of 16 out of a total of 22 stroke patients surviving the first year after surgery. At discharge, 79.4% (n=50) of stroke patients had a mRS score higher than 3. One year after surgery, this rate decreased to 68.8% (n=11) of patients with a score higher than 3.” (Page 15, line 281)
Furthermore, we added the following text to our discussion:
“We observed a low rate of recovery in the long-term follow-up. We cautiously conclude that only few patients recover from a severe postoperative stroke after aortic surgery if symptoms remained until hospital discharge.” (Page 17, line 312)

Comment 6: The limitations section is very cursory. I could think of a few more such as the definition of stroke (excludes TIA, amaurosis, or strokes with resolution within 7 days), the early deaths are excluded, the heterogeneity of the sample (are elective CABG the same as emergent ATAD?), etc. Please revisit.
Reply 6: Thank you for pointing this out. We agree that the limitations need to be revised. We modified the text as advised (see page 22, line 419).
Changes in the text: We changed the text in our limitations section as follows:
“The main limitation of our study is its single-center and retrospective nature. Multicenter analyses are needed. Nevertheless, our study included a high number of patients over a significant time period of ten years. Our cohort is very heterogenic including a broad range of patients presenting with different pathologies and undergoing the whole variety of surgical procedures of the thoracic aorta. However, this could also be seen as a strength as the presented cohort and study results may well represent clinical practice and may substantially improve preoperative risk evaluation of aortic patients. Moreover, our data represents the outcome of a high-

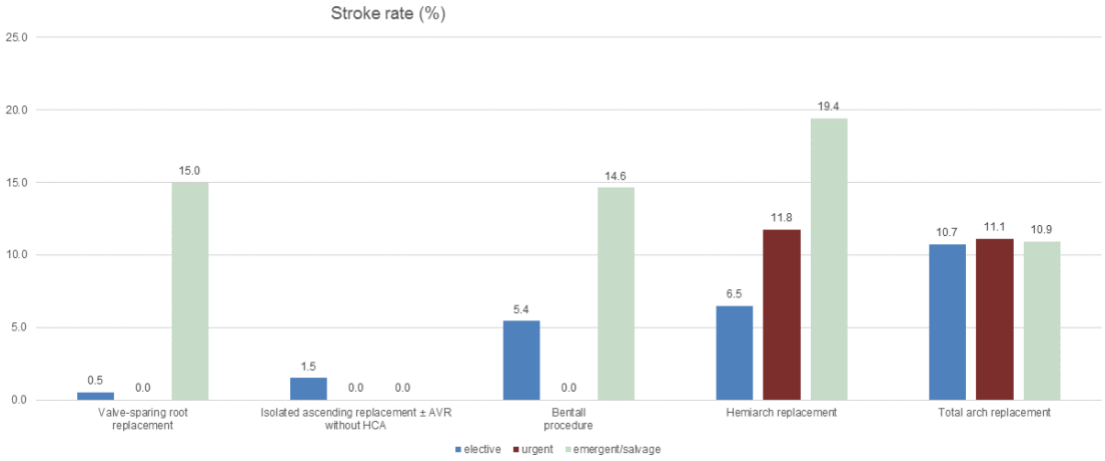
volume aortic center. It is not certain if these results apply to lower volume centers as well.
When defining stroke for our analyses, we did not distinguish between different grades of severity and excluded strokes resolving within 7 days. Also, we excluded patients who died intraoperatively, since it is not possible to evaluate whether these patients suffered from a stroke or not. This might influence our results in either one or the other direction and leading to an over- or underestimation of the stroke risk.
Another limitation regarding the statistical analysis is that only high ECC time correlated with stroke. This might be caused by statistical multicollinearity, as the length of the ECC time correlates with the length of other surgical times (e.g. aortic clamp time or cerebral perfusion time)." (Page 22, line 419)

Comment 7: Well done, interesting and important study overall.
Reply 7: Thank you very much for your kind feedback.
Changes in the text: None.

Comment 8: What percentage of patients had baseline carotid stenosis or had that stenosis previously treated (CEA or stent)?
Reply 8: Thank you for raising this question. We agree that this is an important point. Unfortunately, due to the retrospective design of our study, this data is not available. In general, every elective aortic patient underwent duplex sonography of the extracranial brain-supplying arteries. At our center, one-side asymptomatic severe carotid stenoses are not treated prior to aortic surgery. On the other hand, both-sided or symptomatic carotid stenoses were treated using CEA or stent prior to aortic surgery in elective cases.
Changes in the text: None.

Comment 9: I assume this represents multiple surgeons but please clarify in the methods.
Reply 9: Thank you for raising this very relevant point. During the study period, 25 different cardiac surgeons were performing thoracic aortic procedures at our center. Of these, 5 surgeons were considered aortic surgeons performing more than 20 aortic procedures per year. We adapted the text as advised (see page 7, line 109).
Changes in the text: We added the following text to the methods section:
"These procedures were performed by a total of 25 different cardiac surgeons." (Page 7, line 109)

Comment 10: It may be helpful to separate each column in figure one into three (elective, urgent, emergent).
Reply 10: Thank you for this suggestion. We agree that this adaption of figure 1 could improve the quality of the manuscript. As you can see in the figure below, the stroke rate in urgent procedures is 0% in some procedures. This is because there were only few procedures considered urgent. We therefore decided to show the stroke rate of only two groups (1. Elective, 2. urgent/emergent/salvage). We added this revised figure to our manuscript. (see figure 1)
Changes in the text: We adapted figure 1 accordingly.



Comment 11: While the additional tables are supplementary, it may be useful for the reader to at least discuss the major findings from the supplementary tables in the text (e.g. stroke by weekday/weekend, etc.).

Reply 11: Thank you for this suggestion. In the supplementary material, tables S1-10 show the risk factor analyses for suffering either from an embolic (S1-5) or from a hemodynamic stroke (S6-10). We agree that main results of the supplementary material should be presented in the results section.

Changes in the text: We included the main results of these subgroup risk factor analyses into the results section (see page 14 line 247):

"Further risk factor analyses were performed to identify specific risk factors for the occurrence of embolic or hemodynamic stroke, respectively (Table S1-S10).

Of all postoperative strokes, 59 (62.8%) were of embolic and 23 (24.5%) of hemodynamic origin. Two strokes were caused by hemorrhage. One stroke was considered lacunar. In nine patients, strokes could not be clearly classified.

Risk factor analysis for the occurrence of an embolic stroke identified aortic arch surgery (adjusted OR, 3.95; 95% CI, 2.08-7.51; p<.001), preoperative cerebral malperfusion (adjusted OR, 2.52; 95% CI, 1.10-5.77; p = .028), and concomitant CABG (adjusted OR, 2.09; 95% CI, 1.11-3.96; p=.023) as independent risk factors.

For the occurrence of a hemodynamic stroke, risk factor analysis identified advanced age (adjusted OR, 2.46; 95% CI, 1.02-5.92; p=.046), any atherosclerotic entity (adjusted OR, 2.66; 95% CI, 1.10-6.42; p=.030), ATAD (adjusted OR, 3.92; 95% CI, 1.59-9.66; p=.003) and aortic arch surgery (adjusted OR, 14.26; 95% CI, 1.82-111.74; p=.011) as independent risk factors."

These results were discussed as follows (see page 20 line 378):

"<u>Hemodynamic stroke origin</u>

Advanced age, any atherosclerotic entity, ATAD, and aortic arch surgery were identified as independent risk factors for the occurrence of a hemodynamic stroke. The spectrum of hemodynamic stroke ranges from borderline infarcts due to impaired cerebral microcirculation to massive hypoxic encephalopathy caused by hypoperfusion.

In older patients and patients with atherosclerosis microcirculation in the brain is diminished. In elderly, blood pressure and flow might not be adapted by autoregulation as quickly to changes that occur perioperatively. Already minor

decreases in cerebral blood flow or pressure changes may negatively affect oxygen supply. This leads to insufficient oxygen saturation especially in distal brain areas and watershed strokes may occur. In patients with atherosclerosis this effect might be further enhanced due to relevant stenoses of brain-supplying arteries. In cardiac surgery, intraoperative drops in blood pressure were already found to be a risk factor for watershed stroke (33).

Embolic stroke origin

Apart from arch surgery, subgroup analysis identified concomitant CABG and preoperative cerebral malperfusion as independent risk factors for embolic stroke.
The role of atherosclerosis in the occurrence of embolic strokes during aortic surgery appears complex. In our study, CABG was identified as independent risk factor for the development of an embolic stroke. In these patients, atherosclerosis may not be limited to the coronary arteries but might also affect the aorta as well as the supraaortic and intracranial brain-supplying vessels. Here, especially thrombi formed on ruptured atherosclerotic plaques are a well-known disease mechanism (34). Whether atherosclerotic plaques on their own might be mobilized during aortic surgery and thereby cause embolic strokes is not well investigated so far. Nevertheless, the presence of atherosclerotic plaques in the ascending aorta and the aortic arch is known to be associated with stroke of unknown cause (35).
However, atherosclerosis itself was not found to be an independent risk factor for occurrence of embolic strokes in our analysis. This leads to the assumption, that atherosclerosis during aortic surgery does not mainly increase the stroke risk by causing emboli, but by impairing cerebral microcirculation. In the general population, stroke often is caused by a combination of both atherosclerotic stenotic vessels and embolism of diverse origins (36)."

Comment 12: The histograms at the end are probably not adding much.
Reply 12: Thank you for this comment, we agree and therefore removed the histograms (see supplementary material).
Changes in the text: We removed the histograms from the supplementary material and the corresponding figure legends from the manuscript.

Reviewer D

Comment 1: Materials and methods:
The authors declare that the following article is in accordance with the STROBE reporting checklist.
They start by not following the guideline and report setting (point 5 in STROBE checklist) before study design (point 4).
Please describe the center, instead of writing "our center".
And how comprehensive is the registry?
Study size (point 10) is described after the description of Participants (point 6).
Reply 1: Thank you for pointing this out. We described our center, the German Aortic Center Hamburg, in the methods section. Our registry comprises all patients who were planned to undergo thoracic aortic surgery before starting the procedure, since we included patients based on our digital operating room schedule. Therefore, the rare cases in which the decision to operate on the thoracic aorta was taken intraoperatively

were not included into our database. Besides that, our registry is fully comprehensive. Please also see our reply to comment 2 on your remarks regarding the STROBE checklist.
Changes in the text: We modified the text in the methods section as follows:
"Data from patients undergoing thoracic aortic surgery at the German Aortic Center Hamburg were collected anonymized using our dedicated institutional aortic database and evaluated retrospectively to identify independent risk factors for the occurrence of postoperative stroke. The German Aortic Center Hamburg is a high-volume aortic center in Northern Germany offering the whole spectrum of thoracic aortic procedures. Our registry comprises all patients who were planned to undergo thoracic aortic surgery before starting the procedure, since we included patients based on our digital operating room schedule. Therefore, the rare cases in which the decision to operate on the thoracic aorta was taken intraoperatively were not included into our database. Besides that, our registry is fully comprehensive." (Page 7, line 96)

Comment 2: They're missing several points in the methods section from STROBE checklist. The authors are not following the STROBE checklist.
Please present the information in accordance with STROBE checklist, if you declare this. The order of the presented information is not optional.
Please report p-values with a maximum of decimals of 3.
Reply 2: Thank you for your conscientious reading of our manuscript. We agree with reviewer that each point and the order of the STROBE checklist should be followed. We revised the methods section accordingly (see page 7, line 96) and modified the indication of the p-values (see page 34, table 5).
Changes in the text: Please see methods section. (page 7, line 95)

Comment 3: Discussion: Line 236: This retrospective study did not show what is argued here. It presents an observation of this after the fact that 19 patients who died intraoperatively were excluded. Furthermore the 30 day and 90 day survival analysis is compromised by this. The authors should discuss the effects of this on their results and furthermore in limitation.
Reply 3: Thank you for carefully reading the manuscript. We agree that the retrospective nature of the analysis only allows the identification of associations rather than causal connections. We therefore changed the text accordingly.
Furthermore, we agree that the exclusion of patients that died intraoperatively is an important issue as it remains unclear, whether these deceased patients suffered from intraoperative stroke before their death. Unfortunately, in our opinion, there is no realistic way to discriminate which of these patients had strokes and which didn't, even in a prospective study setting. Nevertheless, this issue clearly remains a limitation of this study. We therefore discussed this point in the limitations section.
Changes in the text: We changed the above-mentioned sentence in the discussion section to: "This study showed an association of a postoperative stroke after thoracic aortic surgery with an impaired early and long-term survival, as demonstrated by Kaplan-Meier-curves and cox regression analyses (Figure 2)." (page 17, line 296)
Furthermore, we added the following text to the limitations section: "Also, we excluded patients who died intraoperatively, since it is not possible to evaluate whether these patients suffered from a stroke or not. This might influence our results

in either one or the other direction and leading to an over- or underestimation of the stroke risk." (Page 22, line 429)

Reviewer E

Comment: This study investigated the risk of postoperative stroke in patients undergoing thoracic aortic surgery. The authors concluded that advanced age, acute type A dissection, arch surgery, concomitant coronary artery bypass grafting and high extracorporeal circulation time were risk factors of postoperative stroke.

This study includes many different procedures including valve sparing root replacement, total arch replacement or descending aortic replacement in order to identify the risk of new postoperative stroke in a cohort undergoing the whole spectrum of thoracic aortic surgery. When considering the risk of postoperative stroke, the difference in these procedures seems to be too influential. Total arch replacement needs cerebral perfusion procedure in addition to circulatory arrest with mild or moderate hypothermia. On the other hand, descending aortic replacement in most cases does not require circulatory arrest, only partial cardiopulmonary bypass and aortic clamp.

Authors considers age, type A aortic dissection, arch surgery, etc. as risks of postoperative stroke, but these are generally reported and cannot be said to be new findings.

When assessing the risk of postoperative stroke in patients undergoing thoracic aortic surgery, it seems meaningful to re-evaluate after unifying surgical procedures. Especially in this study, the numbers of patients who underwent root surgery and arch surgery are large, so it may be meaningful to carefully re-analyze the risk of stroke in those subgroups.

Reply: Thank you for pointing this out. We agree that it can be a limitation that we analyzed a large heterogenic cohort including different procedures and surgical strategies (hypothermic circulatory arrest, cerebral perfusion etc.). We included this in our limitations section. However, in literature mainly studies of subgroups of specific thoracic aortic procedures exist. In our view, it therefore remains rather a strength of our study and the only way to identify stroke risk factors that are independent of the specific procedure to include the whole spectrum of thoracic aortic procedures. Nevertheless, we absolutely agree that analyses of specific subgroups of our cohort may be of great interest. We therefore conducted subgroup analyses of four different cohorts: patients with acute type A dissection, patients with aneurysm, patients undergoing root surgery, and patients undergoing total arch replacement. We could identify the following risk factors:

Acute type A dissection: No independent risk factors identified

Aneurysm: Any atherosclerotic entity, chronic kidney disease, preoperative critical state

Root surgery: Advanced age, acute type A dissection

Total arch replacement: Concomitant coronary artery bypass grafting; Frozen Elephant Trunk procedure in Zone 2 was identified as protective factor

Changes in the text: We added the following text to the limitations section: "Our cohort is very heterogenic including a broad range of patients presenting with different pathologies and undergoing the whole variety of surgical procedures of the thoracic aorta. However, this could also be seen as a strength as the presented cohort

and study results may well represent clinical practice and may substantially improve preoperative risk evaluation of aortic patients."
We added the following text to our statistical analysis section:
"Additionally, we performed subgroup analyses for patients presenting with acute type A dissection, presenting with aneurysm, undergoing root surgery and undergoing total arch replacement." (Page 9 line 157)
Furthermore, we added the following text to our results section:
"Risk factors identified in the subgroup of patients presenting with aneurysm were any atherosclerotic entity, chronic kidney disease, preoperative critical state. In patients with acute type A dissection no risk factors could be identified. Risk factors in patients undergoing root surgery were advanced age and acute type A dissection. In patients undergoing total arch replacement, concomitant coronary artery bypass grafting was a risk factor. Furthermore, in this subgroup, the FET procedure using aortic arch zone 2 as landing zone was revealed to be a protective factor against stroke." (Page 15, line 261).
Please see tables S11-30 in the supplementary material for details on the additional subgroup analyses.

Reviewer F

Comment 1: They identified that preoperative malperfusion was a significant risk factor for embolic stroke but not for hemodynamic stroke, which logically could be the other way around. The speculation for the reason would be interesting for the readers.
Reply 1: Thank you very much for raising this important point. Unfortunately, we do not have any data on this. Our theory is, and we emphasize that this is just an idea, that malperfusion may induce thrombus formation in the false and true lumen preoperatively that not yet cause stroke. Due to hemodynamic changes and/or selective antegrade cerebral perfusion, these thrombi may be dislocated during surgery resulting in postoperative embolic stroke. However, this field is scarcely investigated. We tried to approach this issue, but more studies are needed to further examine underlying mechanisms.
Changes in the text: We added the following text to our discussion:
"Moreover, preoperative cerebral malperfusion was identified as risk factor for embolic, but not for hemodynamic stroke. Cerebral malperfusion may induce thrombus formation in the false and true lumen preoperatively that not yet cause stroke. Due to hemodynamic changes and/or selective antegrade cerebral perfusion, these thrombi may be dislocated during surgery resulting in postoperative embolic stroke. However, this field is scarcely investigated, and more studies are needed to further examine underlying mechanisms." (Page 21, line 409)

Comment 2: Table S5 did not show high aortic clamp time >155min was the risk factor for embolic stroke as the authors described in abstract.
Reply 2: Thank you for pointing this out. In a prior risk model based on preliminary data, high aortic clamp time was identified as risk factor. In our current revised model, it was not. Therefore, we now corrected the text accordingly (page 4, line 68). We apologize for this mistake.
Changes in the text: We changed the text in the abstract as follows:

"Risk factors for embolic stroke were arch surgery, concomitant coronary artery bypass grafting and preoperative cerebral malperfusion." (Page 4, line 68)

Comment 3: As CABG was identified as a risk factor for all strokes, the technique for CABG should be described in the method. Type of graft, the way to make proximal anastomosis could be informative to interpret the result.
Reply 3: Thank you for this very relevant remark. We agree and therefore collected data regarding CABG techniques. Of all patients that underwent concomitant CABG, 99 (55.0%) underwent complete arterial bypass grafting. In 81 patients (45.0%) a central anastomosis to the aorta was performed. Within the group of patients undergoing concomitant CABG, the rate of patients receiving central anastomoses to the aorta was significantly higher in the stroke group (no stroke 41.8% vs stroke 68.2%; *p*=.020).
Changes in the text: We added the following text to our results section:
"As concomitant CABG was identified as independent risk factor, we further analyzed CABG specific procedural data. Of all patients that underwent concomitant CABG, 99 (55.0%) underwent complete arterial bypass grafting. In 81 patients (45.0%) a central anastomosis to the aorta was performed. Within the group of patients undergoing concomitant CABG, the rate of patients receiving central anastomoses to the aorta was significantly higher in the stroke group (no stroke 41.8% vs stroke 68.2%; *p*=.020)." (Page 14, line 239)

Comment 4: As CABG was identified as a risk factor for stroke, the authors have mentioned that PCI might be more favorable option for elderly patients in conclusion. However, considering the requirement of antiplatelet medicine after PCI could be strong limitation for aortic surgery and there was no data supporting this comment in the study, I recommend to revise this sentence.
Reply 4: We would like to thank the reviewer for this very relevant remark. As you mentioned, dual antiplatelet therapy (DAPT) is well known to increase the bleeding risk in cardiac surgery (1,2). Although we do not consider dual antiplatelet therapy (DAPT) as an absolute contraindication for aortic surgery, our data indicates that patients under DAPT (n=28) significantly more often need resternotomy for bleeding than patients without DAPT (DAPT 17.9% vs. no DAPT 6.2%; *p*=.031). However, considering the high risk for stroke in patients with concomitant CABG and as well the high bleeding risk in patients undergoing aortic surgery under DAPT, postponing aortic surgery in elective cases with low risk for spontaneous complications (dissection or rupture) until DAPT after PCI may be discontinued might be an option in selected cases.
Changes in the text: We added the following text to our conclusion section:
"In the case of prior percutaneous coronary intervention (PCI), the risk of bleeding might be increased due to postinterventional dual antiplatelet therapy (DAPT). Therefore, the individual stroke and bleeding risk needs to be evaluated in these patients to decide between concomitant CABG and PCI. Postponing aortic surgery in elective cases with low risk for spontaneous complications (dissection or rupture) until DAPT after PCI may be discontinued might be an option in selected cases." (Page 23, line 445)
<u>References:</u>

1. Hansson EC, Geirsson A, Hjortdal V, et al. Preoperative dual antiplatelet therapy increases bleeding and transfusions but not mortality in acute aortic dissection type A repair. Eur J Cardiothorac Surg 2019;56:182-8.
2. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). European Heart Journal 2017;39:213-60.