Peer Review File

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Response to the Reviewer A's comments

Reviewer A:

Comments		Responses	
C1	- The authors mentioned they used STROBE to report the cohort, but did not mention when the index date was, and what the definition of exposed and control group was. The authors divided the population into three groups: nonstatins, LMDS, and HDS. In the analyses, the authors compared both the LMDS and HDS groups to the nonstatin group. However, in the results, the conclusion also stated "The benefit of LMDS therapy was better than HDS	R1	Thank you for bringing this matter to our attention. We appreciate your comment. We have carefully reviewed the STROBE guideline and made appropriate adjustments to our study to ensure adherence to the guideline. Specifically, we have clearly stated the recruitment and follow-up period of the study population in both the Abstract and Method sections. In addition, we have revised the definitions of the exposed and control groups to reflect that the exposed group consisted of patients receiving statin therapy after stroke onset, while the control group consisted of patients receiving nonstatin therapy. Moreover, we stratified the exposed group into high-dose statins (HDS) and low-to-moderate-dose statins (LMDS), as defined by prior research. We subsequently performed multiple logistic regression analyses as shown in Table 2. The variable "statins" in Table 2 represents nonstatin therapy in comparison to statin therapy, while the "Statin dose"

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<tr><td></td><td>therapy in this cohort." while I did not see a comparison between the LMDS group and the HDS group in the analyses.

What were the index date and the definition of the exposed and the control group in this cohort? How did the authors reach the conclusion that LMDS is better than HDS?</td><td></td><td colspan="2">variable refers to different subgroups of statin use.

The results of Table 2 indicated that statin therapy was superior to nonstatin therapy after multiple logistic regression analysis. And the LMDS group had a higher OR than the HDS group in the statin therapy group (OR=3.68, p=0.0309 vs OR=3.45, p=0.0402) (Table 2).

As you suggested, we further encoded the LMDS as a dummy variable to enable comparison with the HDS group, and we also found that the likelihood of 3-month good functional outcome was comparatively lower in the HDS group than the LMDS group. However, this difference did not reach statistical significance (OR=0.94, p=0.8411) (Table S1).

Therefore, we have revised our conclusion to clarify our research aim and improve its rigor and academic soundness. The revised conclusion reads as follows: “LMDS therapy is associated with favorable impacts on 3-month functional outcomes and a reduced risk of HT compared to non-statin therapy, while no significant differences were observed between LMDS and HDS therapy in our study.” We hope that these revisions have improved the clarity and precision of our research, and we thank you for your valuable input.

<table><tr><td>Before</td><td>After</td></tr></table></td></tr>
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Comments		Responses			
			"This retrospective cohort study included AIS patients who were admitted within 7 days after symptom onset and did not receive reperfusion therapies."	"This retrospective cohort study included AIS patients who were admitted within 7 days after symptom onset and received conventional medication treatment alone from November 2019 to November 2020 in the Neurology, Department of West China Hospital, Sichuan University."	References: Abstract: Page 2 line 8-11
			"The high-dose statins (HDS) were defined as atorvastatin, fluvastatin, lovastatin, simvastatin, and pravastatin >20 mg per day, and rosuvastatin at a dose >10 mg per day. (14) Lower doses were defined as LMDS."	"The exposed group was defined as patients who received statin treatment after admission, while the control group was composed of patients who did not receive statin treatment after stroke onset. For the exposed group, the high-dose statin (HDS) was defined as atorvastatin, fluvastatin, lovastatin, simvastatin, and pravastatin >20 mg per day, and rosuvastatin at a dose >10 mg per day (23). Lower doses were defined as LMDS (24)."	References: Methods: Page 6-7, line 65-70
C2	- The follow-up was conducted on day 90 after admission. However, there were inconsistencies in using the period of	R2	Thank you for your important comment. We have taken into consideration your helpful suggestion and have provided a more comprehensive description of the follow-up period:		

Comments		Responses			
	follow-up whether it was in days or in months which could be different. The mean or median of the duration of follow-up was not reported.		Before	After	
			"The primary outcome was defined as an mRS score at 3 months during clinical follow-up by telephone or mail."	"The mRS at 3 months was assessed through a face-to-face interview or via telephone follow-up with the patients, their relatives, or their general practitioners by a certified neurologist who was blinded to the clinical information. The follow-up period was 3 months after the onset of stroke, with a window period of seven days."	References: Methods: Page 7, line 83-86
C3	- The subjects were included when they were admitted to the hospital within 7 days from stroke onset. Was there a reason behind the cut-off of seven days?	R3	We appreciate the reviewer for bringing up this issue. The 7-day cut-off for patient inclusion in stroke studies is a commonly used time frame in stroke research because it is generally accepted as a reasonable time frame for studying the acute phase of stroke. The rationale behind this cut-off is that patients who are admitted to the hospital within 7 days of stroke onset are more likely to receive timely and appropriate treatment, which may improve their outcomes (1). Several studies have used the 7-day cut-off for patient inclusion in stroke trials (2)(3). For instance, the Japan Stroke Data Bank Investigators conducted a nationwide, hospital-based, multicenter, prospective registry cohort study to determine secular changes in initial neurological severity and short-term functional outcomes of patients with acute stroke by sex, including AIS patients who registered within 7 days after symptom onset (4). Consistent with previous studies, we included AIS patients who registered within 7 days of stroke onset in the present study.		

Comments		Responses	
C4	- In the results, the authors presented independent risk factors for the functional outcome. However, the study's purpose was 'to evaluate the effect of different statin doses on the prognosis of AIS patients without reperfusion therapy." Therefore there was a difference between the study's purpose and the results. By the method of analysis, it became unclear whether the authors wanted to investigate factors influencing the functional outcome, which includes statin doses, or to investigate the association between statin doses and the functional outcome of AIS patients. Why do the authors need to present the risk factors influencing the functional outcome? If the focus was the association between statin doses and the outcomes then why the nonstatin group was also included and why the LMDS group was not compared to the HDS group?	R4	Thank you for your insightful comment. We sincerely apologize for the confusion generated by the previous version of our manuscript. According to your suggestions, we have made the necessary revisions to ensure that our aims and results are presented with utmost clarity. We hope that this revised version will meet with your approval. Firstly, we conducted an assessment of additional factors that could potentially impact the outcomes, aiming to mitigate any potential confounding effects. We adjusted for these confounding factors in the multivariate analysis, so we can investigate whether various influencing factors had an interaction effect with statin use (Figure 2). Secondly, as demonstrated in the manuscript, our primary objective was to assess the efficacy and safety of LMDS in AIS patients who were receiving conventional medication therapy only. However, during our retrospective collection of clinical data, we discovered that 38.84% of AIS patients who were on conventional medication therapy had also received HDS treatment. It would have been biased and failed to represent the real-world clinical practice if we had excluded these patients from our study. Therefore, we included them in our analysis as well. As regard to the comparation between LMDS and HDS in statistical analysis according to encoding LMDS as a dummy variable, we found that the HDS group had a lower likelihood of a favorable functional outcome at 3 months than the LMDS group and a higher risk of HT occurrence (OR=0.94 and OR=1.19, respectively). However, those differences were not statistically significant (p=0.8411 and p=0.7093, respectively). Therefore, we revised those relevant sentences in the conclusion and results section accordingly. We appreciate you for pointing out the issue. We hope that these clarifications have shed more light on our study and the results we

Comments		Responses			
			obtained. Thank you once again for your invaluable feedback.		
			Before	After	
			"Our findings provide evidence for the benefit and safety of LMDS therapy 37 in AIS patients with medication treatment alone. LMDS therapy appears to have a greater effect on 3 months functional outcomes and a lower risk of HT compared to HDS therapy in our study."	"Our findings provide evidence for the benefit and safety of LMDS therapy in AIS patients with medication treatment alone. LMDS therapy is associated with favorable impacts on 3-month functional outcomes and a reduced risk of HT compared to non-statin therapy, while no significant differences were observed between LMDS and HDS therapy in our study. Further studies with prospective design and larger sample sizes are necessary to validate our results."	References: Abstract: page 3, line 24-29
			"The benefit of LMDS therapy was better than that of HDS therapy in this cohort."	"Additionally, we encoded LMDS as a dummy variable to allow for a comparison with the HDS group and found that the HDS group had a reduced likelihood of achieving favorable functional outcomes at 3-month when compared to the LMDS group. However,	References: Results: page 11, line 164-168

Comments		Responses			
				this difference was not statistically significant (OR=0.94, p=0.8411) (Table S1)."	
			-	"After encoding LMDS as a dummy variable, it was observed that the likelihood of HT occurrence was comparatively higher in the HDS group than the LMDS group. However, this difference did not reach statistical significance (OR=1.19, p=0.7093) (Table S1)."	References: Results: page 12-13, line 196-199
C5	- In the discussions, it was stated "The American College of Cardiology/American Heart Association 2013 guideline has recommended using high- and moderate-intensity statins. However, since there was a racial difference in the plasma LDL reduction response and the risk of statin toxicity (Asian have higher blood statin level) between Asian and Caucasian, LMDS is commonly prescribed among Chinese patients except for those with a very high risk of ASCVD."	R5	Thank you for your valuable suggestion, which has helped to improve the quality of our research. We have incorporated your suggestions in our revised manuscript to ensure clarity and precision. Firstly, while high-intensity and high-dose statins use has increased globally over the past decade, in developing countries like China, high-dose and high-intensity statin use is still lower than in western and developed countries (5, 6). And some clinicians may not be familiar with the revised recommendations. For instance, in a survey conducted among 513 medical providers, 34% were unfamiliar with the 2013 protocols. Therefore, doctors may not always follow guideline recommendations when prescribing statins, resulting in low-moderate dose statins being typically prescribed in daily clinical practice (7), especially in Asia countries such as China and Japan (8, 9). Secondly, we considered that the use of statin dosage as a criterion may more		

<table>
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<tr><td></td><td>It seemed it was insinuated that the intensity of statins and the dose of statins were the same things while they were not. The authors defined LMDS and HDS using a study conducted by Marazzi et al. on the post-percutaneous coronary intervention population, not stroke. The authors stated "The HDS were defined as atorvastatin, fluvastatin, lovastatin, simvastatin, and pravastatin >20 mg per day, and rosuvastatin at a dose >10 mg per day. Lower doses were defined as LMDS." However, ACC/AHA defines only atorvastatin >= 40 mg and rosuvastatin >= 20 mg as high-intensity statins. Therefore, in this study, some percentage of patients in the HDS group also used moderate-intensity statins.

Why did the authors define statins based on the dose and not based on the intensity? How this would influence the conclusion or the impact of the study?</td><td></td><td colspan="3">appropriate in our study. Current guidelines focus on LDL cholesterol lowering as the primary target of therapy, and while the definition of statin intensity usually along with lipid-lowering targets. However, in clinical practice in China, there is little follow-up on the achievement of these targets after using a certain dose of statins. Similarly, as a retrospective study, we were unable to obtain this information in many patients. Therefore, using the term "statin intensity" in our study may not be completely accurate.

Based on these considerations, it is reasonable to choose the statin use dosage as a criterion to be more precision and comprehensive, consistent with previous studies in cardiovascular diseases. (8, 10-12).

We acknowledge that the interchangeability of the terms "dosage" and "intensity" may have caused confusion. To address this potential confusion, we have taken care to use consistent terminology throughout our revised manuscript.

We appreciate you bringing this issue to our attention, if we focus on statin intensity, we will prospectively enroll patients and evaluate lipid level at follow-up to investigate whether patients have achieved lipid-lowering targets.

Once again, we appreciate your important comment.

<table><tr><th>Before</th><th colspan="2">After</th></tr><tr><td>-</td><td>“Moreover, based on recently updated lipid management guidelines from China (31), LDL levels remain the primary target for lipid intervention. However, it is difficult to collect detailed information</td><td>References:
Discussion:
Page 15, line 245-252</td></tr></table></td></tr>
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<tr><th colspan="2">Comments</th><th colspan="4">Responses</th></tr>
<tr><td></td><td></td><td></td><td></td><td>on the adherence to statin therapy and whether these patients achieved their lipid-lowering targets in real clinical practice, especially in retrospective studies. Given the urgency of lipid management, prospective cohort studies are necessary to investigate the effect of different statin dosages on lipid-lowering efficacy and adherence to statin therapy in future studies.”</td><td></td></tr>
<tr><td>C6</td><td>- The authors mentioned that the subjects studied were "AIS patients with medication treatment alone" while in earlier parts they were 'AIS patients without reperfusion therapy."
Why did the authors Error! Filename not specified.use the term 'medication treatment alone' when fibrinolytic agents such as alteplase were also a medication that can be used as a method of reperfusion? Please be consistent.</td><td>R6</td><td colspan="3">Thank you for bringing those errors to our attention. We apologize for any confusion caused. We would like to clarify that intravenous thrombolysis (IVT) is also considered a reperfusion therapy. We have re-written the sentences in question to make this point clearer for readers. Thank you for your comment and helping us improve the clarity of our manuscript.
Before | After
“Low-to-moderate dose statins improve the functional outcome of acute ischemic stroke without reperfusion therapy” | “Low-to-moderate dose statin improve the functional outcome of acute ischemic stroke with conventional medication treatment” | References: Title page</td></tr>
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Comments		Responses			
			"However, the correlation between the LMDS use and prognosis has not been evaluated in AIS patients without reperfusion therapies."	"However, the correlation between the LMDS use and prognosis has not been evaluated in AIS patients with conventional medication treatment alone."	References: Abstract: Page 2, line3-5
			"(3) the patients did not receive reperfusion therapies;"	"(3) received conventional medication treatment alone without reperfusion therapies such as intravenous thrombolysis (IVT) or endovascular treatment (EVT);"	References: Methods: Page 6, line46-47

References:

1. Cappellari M, Turcato G, Forlivesi S, et al. Introduction of direct oral anticoagulant within 7 days of stroke onset: a nomogram to predict the probability of 3-month modified Rankin Scale score > 2. J Thromb Thrombolysis. 2018 Oct;46(3):292–8.

2. Wang Y, Liao X, Wang C, et al. Impairment of cognition and sleep after acute ischaemic stroke or transient ischaemic attack in Chinese patients: design, rationale and baseline patient characteristics of a nationwide multicentre prospective registry. Stroke Vasc Neurol. 2021 Mar;6(1):139–44.

3. Wang Y, Jing J, Meng X, et al. The Third China National Stroke Registry (CNSR-III) for patients with acute ischaemic stroke or transient ischaemic attack: design, rationale and baseline patient characteristics. Stroke Vasc Neurol. 2019 Sep;4(3):158–64.

4. Kuwashiro T, Sugimori H, Ago T, Kamouchi M, Kitazono T. Risk factors predisposing to stroke recurrence within one year of non-cardioembolic stroke onset: the Fukuoka Stroke Registry. Cerebrovasc Dis. 2012;33(2):141–9.

5. Liu Y, Lv X, Xie N, et al. Time trends analysis of statin prescription prevalence, therapy initiation, dose intensity, and utilization from the hospital information system of Jinshan Hospital, Shanghai (2012-2018). BMC Cardiovasc Disord. 2020;20(1):1–13.

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7. Joint Committee on the Chinese Guidelines for Lipid Management. Zhonghua Xin Xue Guan Bing Za Zhi. 2023;51(3):221-255.

8. Taguchi I, Iimuro S, Iwata H, et al. High-Dose Versus Low-Dose Pitavastatin in Japanese Patients With Stable Coronary Artery Disease (REAL-CAD): A Randomized Superiority Trial. Circulation. 2018 May;137(19):1997–2009.

9. Mora S, Wenger NK, Demicco DA, et al. Determinants of residual risk in secondary prevention patients treated with high- versus low-dose statin therapy: the Treating to New Targets (TNT) study. Circulation. 2012 Apr;125(16):1979–87.

10. Matyori A, Brown CP, Ali A, Sherbeny F. Statins Utilization Trends and Expenditures in the US Before and After the Implementation of the 2013 ACC/AHA Guidelines. Saudi Pharm J. 2023.

11. Greca E, Kacimi O, Poudel S, et al. Immunomodulatory effect of different statin regimens on regulatory T-cells in patients with acute coronary syndrome: a systematic review and network meta-analysis of randomized clinical trials. Eur Hear journal Cardiovasc Pharmacother. 2023 Feb;9(2):122–8.

12. Kim J-S, Kim J, Choi D, et al. Efficacy of high-dose atorvastatin loading before primary percutaneous coronary intervention in ST-segment elevation myocardial infarction: the STATIN STEMI trial. JACC Cardiovasc Interv. 2010 Mar;3(3):332–9.

Response to the Reviewer B's comments

Reviewer B:

<table>
<tr><th colspan="2">Comments</th><th colspan="4">Responses</th></tr>
<tr><td>C1</td><td>- "Owing to the dose-effect difference to statins between Asians and Caucasians, low-to-moderate-dose statins (LMDS) are more commonly used among Asian patients in clinical practice" – This aspect seems to be really important to justify the importance of the study. Therefore, I suggest the authors provide more information about why they state that there is a difference in the statin use pattern among Asians and Caucasians.</td><td>R1</td><td colspan="3">Thank you for your valuable comment. We agree that emphasizing the difference in statin dose-effect between Asians and Caucasians is crucial to highlight the significance of our study. Based on your suggestion, we have revised the article by including detailed information on the differences in statin use patterns between Asians and Caucasians in the introduction section. We hope that these revisions adequately address your concerns, and we appreciate your comment.</td></tr>
<tr><td></td><td></td><td></td><td>Before</td><td colspan="2">After</td></tr>
<tr><td></td><td></td><td></td><td>"Owing to the dose-effect difference to statins between Asians and Caucasians, low-to-moderate-dose statins (LMDS) are more commonly used among Asian patients in clinical practice."</td><td>"Since Asians are more responsive to the lipid-lowering effects of statins than non-Asians which may be contributed by differences in dosage effects, drug metabolism, body size, and dietary habits, low-to-moderate-dose statin (LMDS) are more commonly prescribed among ASCVD patients in daily clinical practice, particularly in Asia."</td><td>References: Introduction: Page 4, line 13-17</td></tr>
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<tr><th colspan="2">Comments</th><th colspan="4">Responses</th></tr>
<tr><td>C2</td><td>- Do the authors know if there is a study investigating a potential benefit of LMDS in cases of cardiovascular diseases (not cerebrovascular diseases) in the Chinese population? Data from these studies could also be interesting to be mentioned in the “Introduction”.</td><td>R2</td><td colspan="3">Thank you for your constructive suggestion, which have greatly enhanced the clarity and relevance of our research. We have included more information about the use of LMDS therapy in Asian patients with cardiovascular diseases in the Introduction section.<table><tr><td>Before</td><td>After</td><td></td></tr><tr><td>-</td><td>“Evidence has demonstrated that the efficacy of LMDS for cardiovascular disease (CVD) patients in Asian, such as GOALLS study, STATT study, and RAEL-CAD study (9, 13-15)”</td><td>References: Introduction: Page 4. line 17-19</td></tr></table></td></tr>
<tr><td>C3</td><td>- What was the mean follow-up period?</td><td>R3</td><td colspan="3">Thank you for bringing up such an important point. We have taken into consideration your helpful suggestion and have provided a more detailed and precise description of the follow-up period:<table><tr><td>Before</td><td>After</td><td></td></tr><tr><td>“The primary outcome was defined as an mRS score at 3 months during clinical follow-up by telephone or mail.”</td><td>“The mRS at 3 months was assessed through a face-to-face interview or via telephone follow-up with the patients, their relatives, or their general practitioners by a certified neurologist who was blinded to the clinical information. The follow-up period was 3 months after the onset of stroke, with a window period of seven days.”</td><td>References: Methods: Page 7, line 83-86</td></tr></table></td></tr>
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<tr><td>C4</td><td>- Did the authors consider using survival analysis as well?</td><td>R4</td><td colspan="2">Thank you for your thoughtful comment. As you pointed out, survival analysis is an important statistical method that is typically used to model the relationship between an outcome and predictors by analyzing time-to-event outcomes and estimating the probability of experiencing an event over time, such as death or the occurrence of a disease. Unfortunately, in our cohort study, we had a cut-off follow-up period and did not record the precise time until the occurrence of the event of interest. Therefore, we chose to use logistic regression analysis instead of Cox regression analysis. Nonetheless, your suggestion is highly valuable, and it emphasizes the importance of accounting for censored data in further research. We will keep this in mind in our future studies to enhance the quality of our analysis. Thank you once again for your insightful comment.</td></tr>
<tr><td>C5</td><td>- The authors assess the “haemorrhagic transformation” at 3 months. How did the authors differ cases of HT from new haemorrhagic stroke?</td><td>R5</td><td colspan="2">Thank you for your comment. In our study, we differentiated cases of hemorrhagic transformation from new hemorrhagic stroke based on the following criteria: Hemorrhagic transformation: defined as the development of new or worsening hemorrhage within an existing infarcted area on follow-up imaging, with a corresponding clinical presentation (1-3).

New hemorrhagic stroke: defined as the development of a new hemorrhagic lesion on follow-up imaging with a corresponding clinical presentation (4, 5).

We have added this clarification to the Methods section of our manuscript to ensure that this information is clear to readers. Thank you for bringing this to our attention.</td></tr>
<tr><td></td><td></td><td></td><td>Before</td><td>After</td></tr>
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Comments		Responses			
			-	"We defined hemorrhagic transformation (HT) as any degree of hyperdensity within the area of low attenuation in follow-up CT scans within 7 days of admission. The classification of HT was based on the European Cooperative Acute Stroke Study (ECASS) criteria, which divide HT into four subtypes."	References: Method: Page 6, line 60-63
C6	- Are there any current guidelines in China that may have guided the doctors in the decision of prescribing (or not) LMDS or HDS?	R6	Thank you for your comment. In China, the clinical use of LMWH or HDS for the treatment of venous atherosclerotic cardiovascular disease (ASCVD) is guided by the Chinese Guidelines for Lipid Management, which were last updated in March 2023 (6). These guidelines provide recommendations for the use of LMWH or HDS based on the risk of ASCVD. The new guidelines cover lipid management through the life cycle, from children to the elderly, and aim to improve lipid management in China in all aspects for better prevention and treatment of ASCVD by guiding clinical practice. In our study, we followed these guidelines and made the decision to prescribe LMWH or HDS based on the patient's individual clinical condition and the risk-benefit ratio. We have added this information to our manuscript to clarify this point. Thank you for your valuable comment.			
			Before	After	
			-	"Moreover, based on recently updated lipid management guidelines from China (31), LDL levels remain the predominant target for lipid intervention. Nevertheless, obtaining comprehensive information regarding to the	References: Discussion: Page 15, line 245-252

<table>
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<tr><td></td><td></td><td></td><td></td><td>adherence to statin therapy and the attainment of lipid-lowering targets among patients in real clinical practice, particularly in retrospective studies, can be challenging. Given the urgency of lipid management, prospective cohort studies are necessary to investigate the effect of different statin dosages on lipid-lowering efficacy and adherence to statin therapy in future studies.”</td><td></td></tr>
<tr><td>C7</td><td>- Did the authors monitor adverse effects related to statins?</td><td>R7</td><td colspan="3">We are thankful for your thoughtful and thorough review. As our study was retrospective, the individual follow-up information was obtained from our registry study, and it was difficult to gather information on statin-related adverse effects through face-to-face interviews or telephone calls with patients, their relatives, or their general practitioners during follow-up. Due to the substantial amount of missing data on adverse effects related to statins, we did not analyze them to ensure the accuracy and statistical power of our analysis. We have made an essential correction to the limitations section of our manuscript to address this matter and hope that it meets your expectations. Thank you once again.</td></tr>
<tr><td></td><td></td><td></td><td>Before</td><td colspan="2">After</td></tr>
<tr><td></td><td></td><td></td><td>-</td><td>“Finally, due to the absence of data regarding the incidence of statin side effects and adherence to statin therapy at follow-up (46), our evaluation of potential differences in these outcomes between the LMDS group and the HDS group was impeded.”</td><td>References: Discussion: Page 16, line 280-283</td></tr>
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<tr><td>C8</td><td>- The authors discussed that there was a greater benefit of LMDS therapy than HDS therapy. One of the reasons is the difference between Asians and Caucasians regarding the plasma exposure to statins. In line with this finding, the authors should mention that the lipid profile may also be associated the stroke outcomes and may be used to guide decision of which statin to prescribe (the authors must cite doi: 10.1080/01616412.2021.1967677).</td><td>R8</td><td colspan="3">Thank you for your comment, it has greatly enriched our discussion. Your comment has been extremely helpful to us. We have carefully reviewed the article by Dante Morales et al. as you suggested, and have incorporated the necessary discussions in the revised version of our manuscript.

Before: “Firstly, as previously reported, Asians nearly had a greater plasma exposure to statins than Caucasians.”

After: “Firstly, as previously reported, Asians had nearly greater plasma exposure to statins than Caucasians (27). Due to the increased sensitivity of Asians to statins, previous studies have found that lower statin doses could achieve the lowering-LDL-C treatment targets than non-Asians (9).”

References: Discussion: Page 14, line 231-234</td></tr>
<tr><td>C9</td><td>- Did the authors assess the adherence and withdrawal of the statin therapy? If not, they should acknowledge it as a limitation as previous studies have already demonstrated it may influence the stroke outcomes (the authors must cite doi: 10.1007/s10072-020-04790-y)</td><td>R9</td><td colspan="3">We appreciate your attention to detail and your suggestions for improvement. We have incorporated the limitation of lack of adherence and withdrawal of statin therapy into our discussion, which has been helped us to improve the rigor of our study and identify areas for further improvement.

Before: -

After: “Lastly, a prior literature reported a lower rate of adherence in the HDS group in stable coronary artery disease patients than in the LDS group, thereby possibly nullifying some of the effect of HDS relative to LDS therapy (13). This could

References: Discussion: Page 14-15, line 241-245</td></tr>
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Comments		Responses			
				partly explain the lower proportion of favorable outcomes at 3 months in the HDS group observed in our study."	
			-	"Finally, due to the absence of data regarding the incidence of statin side effects and adherence to statin therapy at follow-up (46), our evaluation of potential differences in these outcomes between the LMDS group and the HDS group was impeded."	References: Discussion: Page 16, line 280-283

References:

1. Tan S, Wang D, Liu M, Zhang S, Wu B, Liu B. Frequency and predictors of spontaneous hemorrhagic transformation in ischemic stroke and its association with prognosis. J Neurol. 2014;261(5):905–12.

2. Chen G, Wang A, Zhao X, et al. Frequency and risk factors of spontaneous hemorrhagic transformation following ischemic stroke on the initial brain CT or MRI: Data from the China National Stroke Registry (CNSR). Neurol Res. 2016;38(6):538–44.

3. Jickling GC, Liu D, Stamova B, Ander BP, Zhan X, Lu A, et al. Hemorrhagic transformation after ischemic stroke in animals and humans. J Cereb Blood Flow Metab. 2014;34(2):185–99.

4. Runchey S, McGee S. Does this patient have a hemorrhagic stroke?: clinical findings distinguishing hemorrhagic stroke from ischemic stroke. Jama. 2010;303(22):2280–6.

5. Smith EE, Rosand J, Greenberg SM. Hemorrhagic stroke. Neuroimaging Clin. 2005;15(2):259–72.

6. Joint Committee on the Chinese Guidelines for Lipid Management. Zhonghua Xin Xue Guan Bing Za Zhi. 2023;51(3):221-255.