PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Personalized antiplatelet therapy based on pharmacogenomics in acute ischemic minor stroke and transient ischemic attack: study protocol for a randomised controlled trial
AUTHORS	Zhang, Xiao-guang; Zhu, Xiao-qiong; Xue, Jie; Li, Zhi-zhang; Jiang, Hua-yu; Hu, Liang; Yue, Yun-hua

VERSION 1 - REVIEW

REVIEWER	A/Prof Ann Ranta Department of Medicine University of Otago Wellington New Zealand
REVIEW RETURNED	28-Jan-2019

GENERAL COMMENTS	Thank you for the opportunity to review this protocol paper. Overall, this is a well written paper describing a well-designed study. I did identify a few grammatical errors most of whcih I have tried to outline below, but I would recommend that this is once more proof read by perhaps a native English speaker. Overarching comments: (1) At times it read as if the trial was already completed - if so I am unsure if this would qualify for a protocol paper? Please see details on where this is unclear below. (2) I was a bit unsure about the wording in the sample size calculation and if the authors indeed mean a 5% relative risk reduction compared to usual therapy then I think the sample size may be wrong whcih may require a statistician to review. (3) Discussion could benefit from a few more identified limitations e.g. only Chinese population meaning generalisability will be limited. Minor points: Abstract -this reads as if the trial has already been completed (line 39 "we conducted"). If a typo I would recommend correcting this. -Line 18 suggest removing 'well-deisgned' and instead let the reader make their own decision Introduction -p 4. Line 44: would be more commonly worded as'have shown' -p5 Line 32 - again reads as if trial has been completed Method

	-p5 line 53 - perhaps add 'selection between 'bases' and 'only'? It is good that trial participation is voluntary...however, it is a little scary that this needs to be pointed out. Isn't that a given? -p6 line 248 - should be 'will not be involved' and 'designment' changed to 'design' -p6 line 50 - grammatical error the patients give consent rather than are provided consent - but as already mentioned above could be deleted here. The sentence on clopidogrel genes is awkward and probably not quite right in this section. I do not understand the meaning of the sentences in in line 53-57. Consider rewriting. -p7 line 4 - 'immediately after' is vague - suggest adding a time frame and rewording to make it sound less like consent will not be obtained before patients are randomised. E.g. "Patients are consented and randomised in a 1:1 ratio to intervention or control group as soon as feasible after the diagnosis of TIA or AIMS is made and no later 24 hours after initial symptom onset." -p7 line 32 - what does the loading dose depend on? Why not load everyone with 300 mg Aspirin? Could added detail be provided? -p7 line 39 - should this read 'or' rather than 'and' given that patients get only one of these three options depending on genetic profile rather than all three treatments? -p7 line 44 - wouldn't it be cleaer to just to use a drug option/dose i.e. 75mg Clopidogrel? On what basis would a clinician pick ticagrelor or 150mg Clopidogrel on clinical grounds? -p8 line 11 - It appears that there are more than one secondary outcomes so might need to rewrite this - perhaps 'main secondary?' or will components of the composite not be looked at individually at all? Even if not you do list at least one more endpoint in the subsequent section (safety endpoint); I suppose you could say 'secondary efficacy endpoint.' -p9 line 51 - I found the sample size calculation confusing. It appears that based on the sample you are recruiting you expect a 15% stroke risk in the control group and a 10% stroke risk in the intervention group, is that correct? If so then wouldn't it be an absolute risk reduction of 5% rather than a relative risk reduction of 5%? To me a RR of 5% from 15% absolute risk would a drop in risk to 14.25% and I would argue that this is (a) not clinically meaningful and (b) would require a much larger sample size. Furthermore, if the 1-year CHANCE trial event rate was 10.6% then what are you basing your assumption on that your control group's 1-year event rate will be 15%? I may well be missing the point and suggest a statistician give this a read over. Quite possibly just semantics. -p9 line 25 - would change to 'preferred short term treatment...for many clinicians.' - I'd argue that there is a still a bit of controversy here especially for longer-term treatment. -p9 line 50 - clopidogrel is not the only approved antiplatelet medication used with Aspirin - Dipyridamole is also approved - could rewrite as 'high-potency short term dual antiplateleyt therapy' which I think is what you mean. -p10 line 13 - good to consider geographic and ethnic differences...but still uncertain how this might apply to non Chinese.

REVIEWER	Zhi-Chun Gu Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China
REVIEW RETURNED	31-Jan-2019

GENERAL COMMENTS	Major comments: This study protocol for randomized controlled trial mainly evaluates personalized antiplatelet therapy based on pharmacogenomics in AIMS and TIA. It is true that there have been no reports on individualized antiplatelet therapy for AIMS and TIA according to the genetic testing. In General, this study is relatively neoteric and well designed, but main limitation of the present study is its value and significance. In addition, it is controversial that correlation between pharmacogenetics of clopidogrel and its efficacy. The pharmacogenetics of clopidogrel is considered unimportant in some studies, especially the double antiplatelet combining aspirin with clopidogrel. In order to make this study more powerful, the author can add new evidence that value of personalize antiplatelet therapy based on pharmacogenetic data to reduce the risk of stroke recurrence in cardiovascular and cerebrovascular diseases into discussion. Whereas, regarding the actual value of antiplatelet therapy in AIMS and TIA, this study protocol might be considered for publication after major revision. The following minor comments should be addressed by the authors. Minor comments: 1. In methods and analysis part, the author described “open blinded RCT”, I'm sorry that I cannot understand the meaning of “open blinded RCT”, the author has to explain in detail. 2. The latest definitions of clopidogrel resistance are high on-treatment platelet reactivity (HPR), so clopidogrel resistance should be instead of high on-treatment platelet reactivity (HPR). 3. The present CPIC guideline is out of date, whether the updated issue keeps the consistent statement? 4. In introduction section, carriers of CYP2C19 loss of function alleles patients with ACS advised to increase the dose of clopidogrel, In the updated study (Ref: Gene variants in responsiveness to clopidogrel have no impact on clinical outcomes in Chinese patients undergoing percutaneous coronary intervention-a multicenter study), this method have not been proven effective. 5. In method design section, the author has to confirm that the double dose of clopidogrel and the use of ticagrelor have been involved in the label or not. In the PLATO trial, ticagrelor increased the No-CABG bleeding compared to clopidogrel. Thus, whether the study has considered the safety for ticagrelor due to the higher bleeding risk than clopidogrel. In addition, the antiplatelet effect of ticagrelor is strong, what measures will be taken in case of bleeding. 6. In section of patients and public involvement, what is the meaning of “We will not perform the structural evaluation on study patients’ burden in RCTs”? The author has to explain it. 7. In the section of randomization and treatments, “Patients randomly assigned to the pharmacogenetic group receive different dose of clopidogrel”. In my opinion, the grouping here can be clearer and more concise, for example, patients in the pharmacogenetic group were assigned to receive different dose of clopidogrel according to genetic test results. 8. The CYP2C19 poor metabolizers type accounts for about 12-15% in the Chinese population, these people will be given

	ticagrelor 90mg twice daily. However, AIMS and TIA are not approved in the indications of ticagrelor, whether this treatment strategy is reasonable. 9. In the section of randomization and treatments, “For standard group, the P2Y12 receptor antagonist is selected by the clinician”, which means control group might use double-dosed clopidogrel or ticagrelor? Please illustrate it in detail. 10. The author claimed that the P2Y12 receptor antagonist is selected by the clinician according to the clinical features of the patients including age, weight, ischemic risk, prior history of stroke/TIA, bleeding risk, and so on. The authors need to elaborate on specific strategy to dose adjustment according to clinical characteristics including every factor mentioned in the article. 11. In sample size section, the calculated sample size is 1,134 patients in each group, it is necessary that the lost rate should be considered in sample size. So, 1,134 patients in each group may be not enough for this RCT study. 12. The statistical analyses section, it is not comprehensive that baseline characteristics are compared between two study groups using T test, $\chi 2$ test is also included in statistical analyses. 13. In the discussion section, please state the genotype-guided antiplatelet therapy trial in the filed of cardiovascular disease. In addition, the SOCRATES (NCT01994720) trial and interim result of PRINCE trial may be useful for deep discussion.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: A/Prof Ann Ranta

Institution and Country: Department of Medicine - University of Otago - Wellington - New Zealand

Overarching comments:

(1) At times it read as if the trial was already completed - if so I am unsure if this would qualify for a protocol paper? Please see details on where this is unclear below.

Re: Thank you for your kind suggestion. We are sorry for making it confusing because of our grammatical errors somewhere. Actually, we registered this clinical trial in December 2018, and just started to implement this trial last month.

(2) I was a bit unsure about the wording in the sample size calculation and if the authors indeed mean a 5% relative risk reduction compared to usual therapy then I think the sample size may be wrong which may require a statistician to review.

Re: Thank you for your kind suggestion. We have already referred to a statistician to give this a read over and have revised the manuscript accordingly. We indeed expect an absolute rather than a relative risk reduction of 5% and the recalculated sample size is 1,191 patients in each group considering a missed follow-up rate around 5%. The details about our basis and the methods of sample size calculation are described below.

(3) Discussion could benefit from a few more identified limitations e.g. only Chinese population meaning generalisability will be limited.

Re: Thank you for your kind suggestion. We have revised the limitations accordingly as follow: Another limitation is that the trial implementation is not multi-centered and only Chinese population are included, which might limit its generalisability.

Minor points:

Abstract

-this reads as if the trial has already been completed (line 39 "we conducted"). If a typo I would recommend correcting this.

Re: Thank you for your kind suggestion. We have revised the manuscript accordingly.

-Line 18 suggest removing 'well-designed' and instead let the reader make their own decision

Re: Thank you for your kind suggestion. We have removed the word “well-designed” in the manuscript accordingly.

Introduction

-p 4. Line 44: would be more commonly worded as 'have shown'

-p5 Line 32 - again reads as if trial has been completed

Re: Thank you for your kind suggestion. We have revised the manuscript accordingly in the revised paper.

Method

-p5 line 53 - perhaps add 'selection between 'bases' and 'only'? It is good that trial participation is voluntary...however, it is a little scary that this needs to be pointed out. Isn't that a given?

Re: Thank you for your kind suggestion. We have revised the manuscript accordingly in the revised paper. As voluntariness is a premise in our trial and indeed not necessary to be pointed out, so we have deleted the sentence “Participation in this clinical trial is voluntary”.

-p6 line 248 - should be 'will not be involved' and 'designment' changed to 'design'

Re: Thank you for your kind suggestion. We have revised the manuscript accordingly in the revised paper.

-p6 line 50 - grammatical error the patients give consent rather than are provided consent - but as already mentioned above could be deleted here. The sentence on clopidogrel genes is awkward and probably not quite right in this section. I do not understand the meaning of the sentences in in line 53-57. Consider rewriting.

Re: Thank you for your kind suggestion. We have revised the manuscript accordingly as follow: The individual genetic information and the corresponding anti-platelet aggregation drug adjustment regimen will be disseminated to study participants as soon as possible after the gene detection. Satisfaction of the intervention and the burden of involvement in this RCT will be assessed as part of the evaluation.

-p7 line 4 - 'immediately after' is vague - suggest adding a time frame and rewording to make it sound less like consent will not be obtained before patients are randomized. E.g. "Patients are consented and randomized in a 1:1 ratio to intervention or control group as soon as feasible after the diagnosis of TIA or AIMS is made and no later 24 hours after initial symptom onset."

Re: Allow us to thank you for your enlightening suggestion. We have revised the manuscript accordingly.

-p7 line 32 - what does the loading dose depend on? Why not load everyone with 300 mg Aspirin? Could added detail be provided?

Re: Thank you for your kind suggestion. The loading dose of Aspirin we originally plan to adopt depends on the PRINCE trial conducted by professor Yong-jun Wang with a dose of 100 – 300 mg. [Wang Y, Lin Y, Meng X, et al. Effect of ticagrelor with clopidogrel on high on-treatment platelet reactivity in acute stroke or transient ischemic attack (PRINCE) trial: Rationale and design. Int J Stroke. 2017;12(3):321-325.] Considering their study is multi-centered while ours is single-centered, and in order to minimize selection bias and control the number of variables, we decide to choose 300 mg as a loading dose of Aspirin.

-p7 line 39 - should this read 'or' rather than 'and' given that patients get only one of these three options depending on genetic profile rather than all three treatments?

Re: Thank you for your kind suggestion. We have revised the manuscript accordingly in the revised paper.

-p7 line 44 - wouldn't it be clear to just to use a drug option/dose i.e. 75mg Clopidogrel? On what basis would a clinician pick ticagrelor or 150mg Clopidogrel on clinical grounds?

Re: Thank you for your kind suggestion. For patients who have adverse reactions of clopidogrel, such as gastrointestinal discomfort, skin rashes and so on, or who receive dual antiplatelet therapy of aspirin and clopidogrel underwent percutaneous coronary intervention (PCI) or myocardial infarction also occur TIA or AIMS or who have poor inhibition of platelet aggregation suggested by thromboelastogram, we may choose ticagrelor. For patients who have poor antiplatelet aggregation with conventional doses of clopidogrel and at the same time have contraindications to ticagrelor, we may consider doubled dosage of clopidogrel.

-p8 line 11 - It appears that there are more than one secondary outcomes so might need to rewrite this - perhaps 'main secondary?' or will components of the composite not be looked at individually at all? Even if not you do list at least one more endpoint in the subsequent section (safety endpoint); I suppose you could say 'secondary efficacy endpoint.'

Re: Special thanks to you for your good comments. We have rewritten the part about secondary outcomes to make it clear: The secondary efficacy endpoint is analyzed as individual or the composite outcomes of the new clinical vascular event (ischemic stroke, hemorrhagic stroke, myocardial infarction, or vascular death).

-p9 line 51 - I found the sample size calculation confusing. It appears that based on the sample you are recruiting you expect a 15% stroke risk in the control group and a 10% stroke risk in the intervention group, is that correct? If so then wouldn't it be an absolute risk reduction of 5% rather than a relative risk reduction of 5%? To me a RR of 5% from 15% absolute risk would a drop in risk to 14.25% and I would argue that this is (a) not clinically meaningful and (b) would require a much larger sample size. Furthermore, if the 1-year CHANCE trial event rate was 10.6% then what are you basing your assumption on that your control group's 1-year event rate will be 15%? I may well be missing the point and suggest a statistician give this a read over. Quite possibly just semantics.

Re: Thank you for your kind suggestion. We have already referred to a statistician to give this a read over. I am sorry that we have some ambiguity in semantic expression. What we really want to express is that we expect a 15% stroke risk in the control group and a 10% stroke risk in the intervention group. It is an absolute risk reduction of 5% rather than a relative risk reduction of 5%. The reason why the event rate in our study is supposed to be higher than that in CHANCE trial is that the patients

we enroll are those with symptoms occurring less than 72 h after the onset of minor ischemic stroke or high-risk TIA, whereas the patients enrolled in CHANCE trial were those with symptoms occurring within 24 hours after the onset of minor ischemic stroke or high-risk TIA. Given that the time point when patients start to receive treatments in our study is later than that in the CHANCE trial and there is no authoritative study at present focusing on the stroke incidence rate during 1 year follow-up for patients with AIMS or TIA occurring less than 72 h, we estimate a higher incidence of primary efficacy endpoint and define it as 15%. As we expect an absolute risk reduction of 5% in the pharmacogenomic group, so we define it as 10%. Then the number of patients we will recruit is based on the incidence of primary efficacy endpoint mentioned above.

-p9 line 25 - would change to 'preferred short term treatment...for many clinicians.' - I'd argue that there is a still a bit of controversy here especially for longer-term treatment.

Re: Thank you for your kind suggestion. We have revised the manuscript accordingly in the revised paper.

-p9 line 50 - clopidogrel is not the only approved antiplatelet medication used with Aspirin - Dipyridamole is also approved - could rewrite as 'high-potency short term dual antiplateleyt therapy' which I think is what you mean.

Re: Thank you for your kind suggestion. It is my cognitive error for the expression that clopidogrel is the only approved antiplatelet medication used with Aspirin. Actually, what I really want to express is that clopidogrel is currently the most widely used antiplatelet agent for AIMS or TIA with aspirin. Logically, we then elaborate the differences in reactivity of clopidogrel among individuals. We have revised the manuscript accordingly in the revised paper.

-p10 line 13 - good to consider geographic and ethnic differences...but still uncertain how this might apply to non Chinese.

Re: Allow us to thank you for your enlightening suggestion. Unfortunately, it is currently only a single-center study so that the sample diversity is limited, but if our present research can find a significant difference in personalized approach to selecting antiplatelet therapy for TIA or AIMS patients, we will extend it to more national minorities and even different countries. Future studies will focus on these issues.

Reviewer: 2

Reviewer Name: Zhi-Chun Gu

Institution and Country: Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China

Minor comments:

1. In methods and analysis part, the author described “open blinded RCT”, I'm sorry that I cannot understand the meaning of “open blinded RCT”, the author has to explain in detail.

Re: Thank you for your kind suggestion. We are sorry that we have made a mistake in the description of RCT. We have checked and made correction in this revision as follow: a prospective, open-label RCT.

2. The latest definitions of clopidogrel resistance are high on-treatment platelet reactivity (HPR), so clopidogrel resistance should be instead of high on-treatment platelet reactivity (HPR).

Re: Allow us to thank you for your enlightening suggestion. We have revised the manuscript accordingly in the revised paper.

3. The present CPIC guideline is out of date, whether the updated issue keeps the consistent statement?

Re: Thank you for your kind suggestion. Unfortunately, we find that the CPIC guideline for CYP2C19 genotype and clopidogrel therapy has not renovated in recent years. From the recent researches about genotype-guided antiplatelet therapy after percutaneous coronary intervention, increasing the dose of clopidogrel or alternative antiplatelet therapy is recommended, which is keeping the consistent statement. [Cavallari LH, Lee CR, Beitelshees AL, Cooper-DeHoff RM, Duarte JD, Voora D, et al. Multisite Investigation of Outcomes With Implementation of CYP2C19 Genotype-Guided Antiplatelet Therapy After Percutaneous Coronary Intervention. JACC Cardiovasc Interv. 2018 Jan 22;11(2):181-191.] [Shen DL, Wang B, Bai J, Han Q, Liu C, Huang XH, Zhang JY. Clinical Value of CYP2C19 Genetic Testing for Guiding the Antiplatelet Therapy in a Chinese Population. J Cardiovasc Pharmacol. 2016 Mar;67(3):232-6.]

4. In introduction section, carriers of CYP2C19 loss of function alleles patients with ACS advised to increase the dose of clopidogrel, In the updated study (Ref: Gene variants in responsiveness to clopidogrel have no impact on clinical outcomes in Chinese patients undergoing percutaneous coronary intervention-a multicenter study), this method have not been proven effective.

Re: The reviewer has made a very good point here. Although this method was reported to have no effect in Wang's study (Ref: Gene variants in responsiveness to clopidogrel have no impact on clinical outcomes in Chinese patients undergoing percutaneous coronary intervention-a multicenter study), another trial reported that individual antiplatelet therapy guided by CYP2C19 genetic testing significantly reduced the rate of major adverse cardiovascular events without an increase in the rate of bleeding in the near term in this Chinese population. [Shen DL, Wang B, Bai J, Han Q, Liu C, Huang XH, Zhang JY. Clinical Value of CYP2C19 Genetic Testing for Guiding the Antiplatelet Therapy in a Chinese Population. J Cardiovasc Pharmacol. 2016 Mar;67(3):232-6.] The inconsistent results of above studies might be attributed to a majority of factors, such as the regions, gene variants and clinical features of patients. So, further studies concerning the effect of an increased dose of clopidogrel on carriers of CYP2C19 loss of function alleles patients with ACS are still needed. However, there have been no reports on individualized antiplatelet therapy for AIMS and TIA according to the genetic testing, therefore our study can provide evidence in this field.

5. In method design section, the author has to confirm that the double dose of clopidogrel and the use of ticagrelor have been involved in the label or not. In the PLATO trial, ticagrelor increased the No-CABG bleeding compared to clopidogrel. Thus, whether the study has considered the safety for ticagrelor due to the higher bleeding risk than clopidogrel. In addition, the antiplatelet effect of ticagrelor is strong, what measures will be taken in case of bleeding.

Re: Thank you for your kind suggestion. We did find that ticagrelor intervention in the PLATO trial compared with clopidogrel was reported to significantly reduce the rate of death from vascular causes, myocardial infarction, or stroke without an increase in the rate of overall major bleeding,but increase the rate of non-procedure-related bleeding. [Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA; PLATO Investigators, Freij A, Thorsén M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361(11):1045-57.] However, the patients included in their study are different from ours, that is, they included patients with an acute coronary syndrome, with or without ST-segment elevation but patients who receive ticagrelor in our study are those with AIMS or TIA accompanied with poor metabolizers of clopidogrel gene. Furthermore, they did not check the clopidogrel gene. We will inform patients the benefits and risks before they are enrolled. Once the patients have bleeding or other adverse reactions, we will

deal with it immediately according to the patient's condition and their tests will be terminated if severe complications happen.

6. In section of patients and public involvement, what is the meaning of “We will not perform the structural evaluation on study patients’ burden in RCTs”? The author has to explain it.

Re: Thank you for your kind suggestion. We are sorry for failing to make ourselves understood and have revised the manuscript accordingly as follow: Satisfaction of the intervention and the burden of involvement in this RCT will be assessed as part of the evaluation.

7. In the section of randomization and treatments, “Patients randomly assigned to the pharmacogenetic group receive different dose of clopidogrel”. In my opinion, the grouping here can be clearer and more concise, for example, patients in the pharmacogenetic group were assigned to receive different dose of clopidogrel according to genetic test results.

Re: Thank you for your kind suggestion. In the section of randomization and treatments, we depicted as follow: Patients randomly assigned to the pharmacogenetics group receive a dose of 75 mg clopidogrel per day (UM and EM group), 150 mg clopidogrel per day (IM group) or ticagrelor 90 mg twice daily (PM group) on days 2 to 21. As the pharmacogenetic group is supposed to involve both clopidogrel and ticagrelor, so we think it might be better to simply describe the specific medications in different pharmacogenetic group.

8. The CYP2C19 poor metabolizers type accounts for about 12-15% in the Chinese population, these people will be given ticagrelor 90mg twice daily. However, AIMS and TIA are not approved in the indications of ticagrelor, whether this treatment strategy is reasonable.

Re: Thank you for your kind suggestion. Although AIMS and TIA have not been approved in the indications of ticagrelor, but as a prospective clinical trial, our trial has been registered at the National Clinical Registration Center and approved by the Ethics Committee. Moreover, the patient’s informed consent will be obtained before execution. In addition, in the PRINCE trial conducted by professor Yong-jun Wang [Wang Y, Lin Y, Meng X, et al. Effect of ticagrelor with clopidogrel on high on-treatment platelet reactivity in acute stroke or transient ischemic attack (PRINCE) trial: Rationale and design. Int J Stroke. 2017;12(3):321-325.], ticagrelor was also used in combination with aspirin in AIMS and TIA, which might further support the rationality of our treatment strategy.

9. In the section of randomization and treatments, “For standard group, the P2Y12 receptor antagonist is selected by the clinician”, which means control group might use double-dosed clopidogrel or ticagrelor? Please illustrate it in detail.

Re: Thank you for your kind suggestion. For this question, the answer is yes since different doses of clopidogrel and ticagrelor can be adopted in both pharmacogenetics and standard group according to their clinical characteristics which are needed to be taken into account for all the patients included. For patients who have adverse reactions of clopidogrel, such as gastrointestinal discomfort, skin rashes and so on, or who receive dual antiplatelet therapy of aspirin and clopidogrel underwent percutaneous coronary intervention (PCI) or myocardial infarction also occur TIA or AIMS or who have poor inhibition of platelet aggregation suggested by thromboelastogram, we may choose ticagrelor. For patients who have poor antiplatelet aggregation with conventional doses of clopidogrel and at the same time have contraindications to ticagrelor, we may consider doubled dosage of clopidogrel.

10. The author claimed that the P2Y12 receptor antagonist is selected by the clinician according to the clinical features of the patients including age, weight, ischemic risk, prior history of stroke/TIA, bleeding risk, and so on. The authors need to elaborate on specific strategy to dose adjustment according to clinical characteristics including every factor mentioned in the article.

Re: Thank you for your kind suggestion. According to the 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke [Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2018 Mar;49(3):e46-e110.], patients with minor stroke who can be treated within 24 hours after the onset of symptoms, the combination of clopidogrel and aspirin per day on days 2 through 21 is advised. Conventional dose advised is 100mg aspirin and 75mg clopidogrel. Actually, clinicians make different anti-platelet strategies based on various factors of the patients, rather than a single factor in clinical practice, and there has been no explicit guideline on how to adjust the dosage of antiplatelet drugs according to clinical characteristics at present. We also consulted Professor Dong Qiang in Huashan hospital, who also believes that it is entirely up to the clinical experience of clinicians and the clinical characteristics of patients to adjust treatment. For example, on condition that a middle-aged patient with a previous history of PCI has recurrent cerebral infarction after long-term oral administration of aspirin and clopidogrel, we may advise him to increase the dosage of clopidogrel or change to ticagrelor. But if he is 90 years old at the same time, changes on the therapeutic regimen of clopidogrel will not be advised. In another case, if he is 50 years old, but with substantial cerebral microbleeds indicated by the susceptibility weighted imaging, we may not recommend the dual antiplatelet therapy and will withdraw him from the trial. Therefore, it is quite difficult for us to elaborate the specific strategies including every factor mentioned above for dose adjustment according to clinical characteristics. The individual differences of patients are so large that the adjustments involved in the clinic vary from person to person. Taking it into account, antiplatelet therapeutic regimen will be made by two fixed senior doctors so as to minimize selection bias in the clinical practice.

11. In sample size section, the calculated sample size is 1,134 patients in each group, it is necessary that the lost rate should be considered in sample size. So, 1,134 patients in each group may be not enough for this RCT study.

Re: The reviewer has made a very good point here. The missed follow-up rate we define it as 5%, so the recalculated sample size is 1,191 patients in each group.

12. The statistical analyses section, it is not comprehensive that baseline characteristics are compared between two study groups using T test, $\chi 2$ test is also included in statistical analyses.

Re: We agreed with your opinion that the $\chi 2$ test is also included in statistical analyses. We have revised the manuscript accordingly in the revised paper.

13. In the discussion section, please state the genotype-guided antiplatelet therapy trial in the field of cardiovascular disease. In addition, the SOCRATES (NCT01994720) trial and interim result of PRINCE trial may be useful for deep discussion.

Re: Allow us to thank you for your enlightening suggestion. We have revised the manuscript accordingly in the revised paper.

VERSION 2 – REVIEW

REVIEWER	Annemarei (Anna) Ranta University of Otago, Wellington, New Zealand
REVIEW RETURNED	19-Mar-2019

GENERAL COMMENTS	Thank you for this excellent resubmission. I am happy that all of my concerns have been adequately addressed. A minor comment

	for the editorial team: it would be helpful if line numbers were included in revised manuscript to more easily spot areas for requested revision. Thank you.

REVIEWER	Zhi-Chun Gu Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China
REVIEW RETURNED	07-Mar-2019

GENERAL COMMENTS	I would like to thank the authors for considering and addressing my comments. The manuscript has been improved. The present status could be considered for publication in BMJ Open.